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(54) Title: IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES					
(57) Abstract <p>A class of substituted imidazole, triazole and tetrazole derivatives are selective agonists of 5-HT₁- like receptors and are therefore useful in the treatment of clinical conditions, in particular migraine and associated disorders, for which a selective agonist of these receptors is indicated.</p>					

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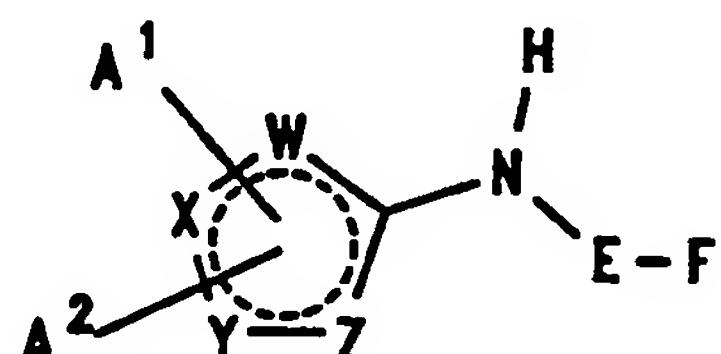
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IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES

The present invention relates to a class of substituted imidazole, triazole and tetrazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT₁-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

5-HT₁-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke *et al.*, The Lancet, 1988, Vol. 1, 1309-11). The compounds of the present invention, being selective 5-HT₁-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

two, three or four of W, X, Y and Z represent nitrogen and the remainder represent carbon provided

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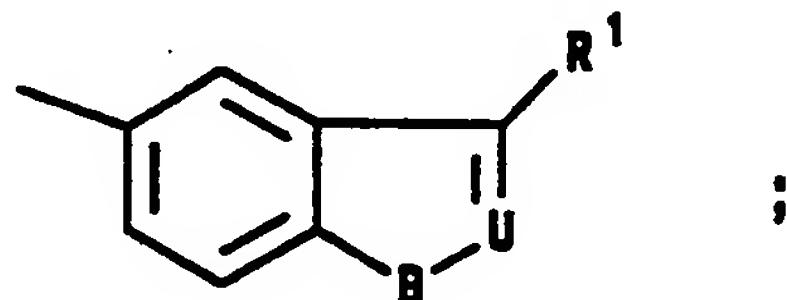
that, when two of W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring;

5 A¹ represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY, -NR^XCO₂RY, -NR^XSO₂RY, or -NR^ZCTN^XRY;

10 A² represents a non-bonded electron pair when all four of W, X, Y and Z represent nitrogen; or, when two or three of W, X, Y and Z represent nitrogen and the remainder represent carbon, A² represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY, -NR^XCO₂RY, 15 -NR^XSO₂RY, or -NR^ZCTN^XRY;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



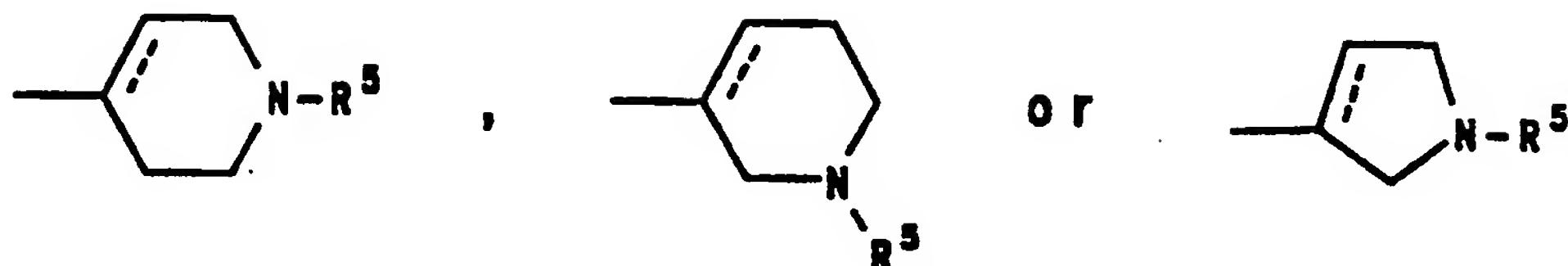
U represents nitrogen or C-R²;

B represents oxygen, sulphur or N-R³;

R¹ represents -CH₂.CHR⁴.NR⁶R⁷ or a group of

30 formula

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in which the broken line represents an optional chemical bond;

R^2 , R^3 , R^4 , R^5 , R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group;

R^z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula $=N.G$; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid,

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tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

5 The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl and aryl(C₁₋₆)alkyl.

10 15 The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

20 25 Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl and t-butyl.

30 Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

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Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

5 Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

A particular aryl group is phenyl.

10 Particular aryl(C₁₋₆)alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

15 Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

20 Particular heteroaryl(C₁₋₆)alkyl groups include pyridylmethyl and pyrazinylmethyl.

25 The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, adamantyl, phenyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, aryloxy, keto, C₁₋₃ alkylenedioxy, nitro, cyano, carboxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkylcarbonyloxy, arylcarbonyloxy, C₂₋₆ alkylcarbonyl, arylcarbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, NR^vR^w, -NR^vCOR^w, -NR^vCO₂R^w, -NR^vSO₂R^w, -CH₂NR^vSO₂R^w, -NHCONR^vR^w, -CONR^vR^w, -SO₂NR^vR^w and -CH₂SO₂NR^vR^w, in which R^v and R^w independently represent hydrogen, C₁₋₆ alkyl, aryl or aryl(C₁₋₆)alkyl, or R^v and R^w together represent a C₂₋₆ alkylene group.

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When R^x and R^y , or R^v and R^w , together represent a C_{2-6} alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

5 When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro, $-COR^x$, $-CO_2R^x$ or $-SO_2R^x$, in which R^x is as defined above.

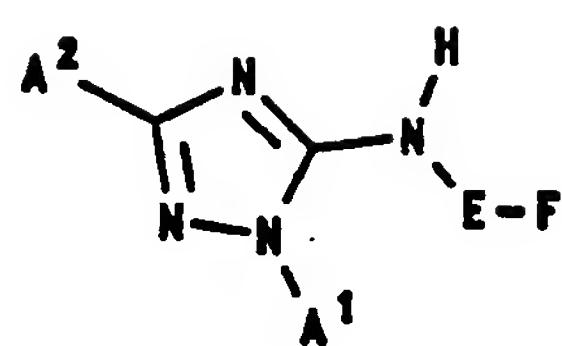
10 The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

15 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

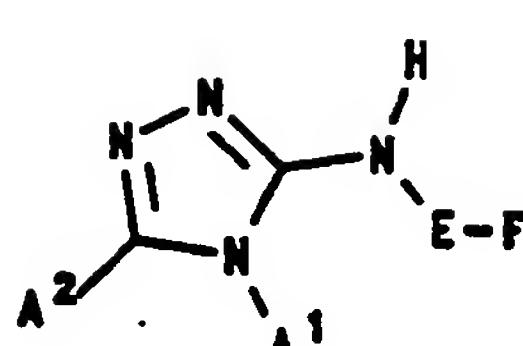
20 Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is 25 to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

30 It will be appreciated that the imidazole, triazole and tetrazole rings of formula I can exist in a variety of isomeric forms having different substitution patterns. These may suitably be represented by formulae IA to IL as follows:

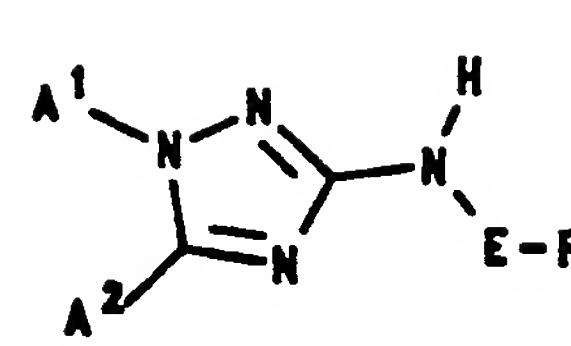
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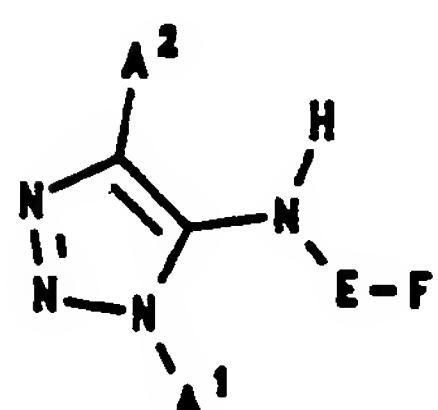
(IA)



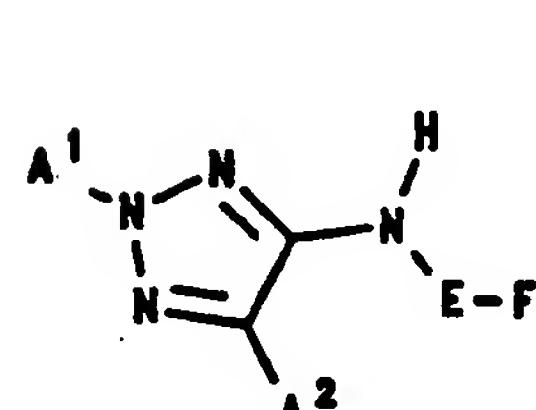
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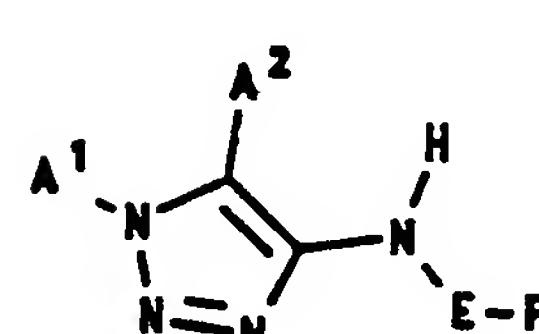
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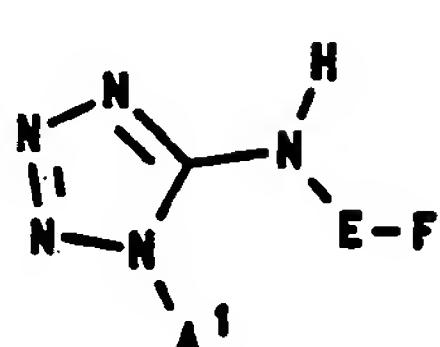
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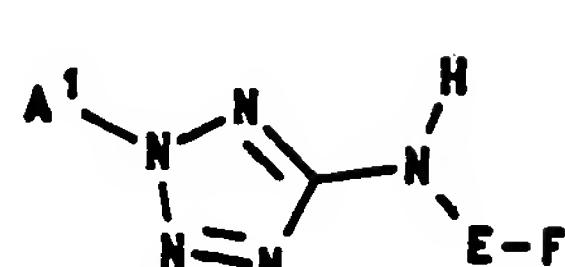
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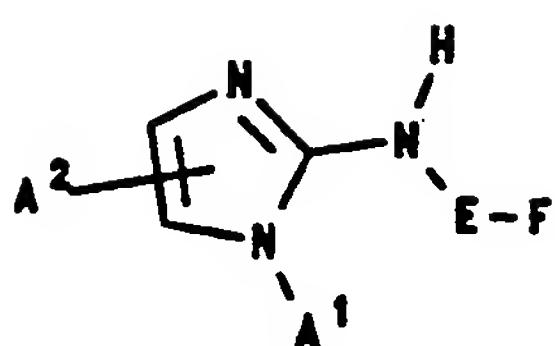
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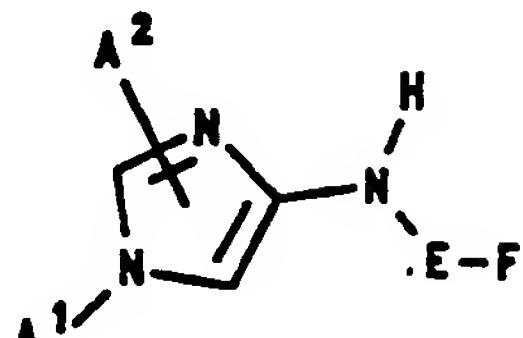
(IG)



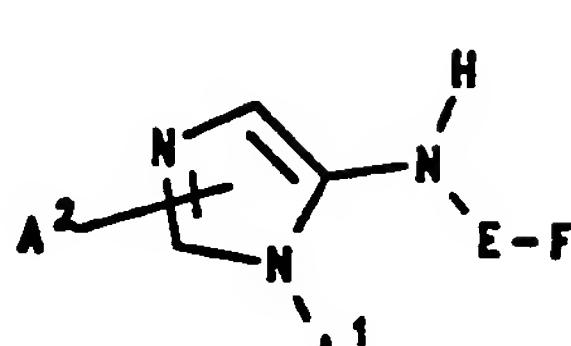
(IH)



(IJ)



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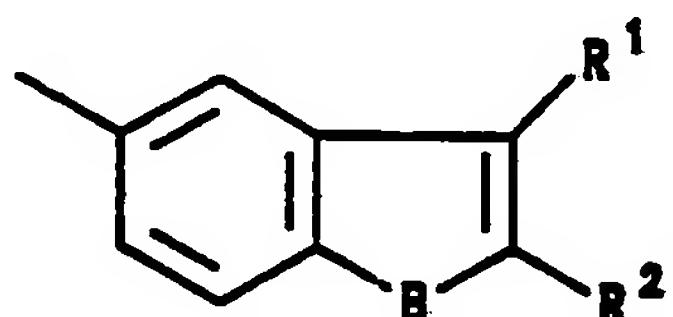
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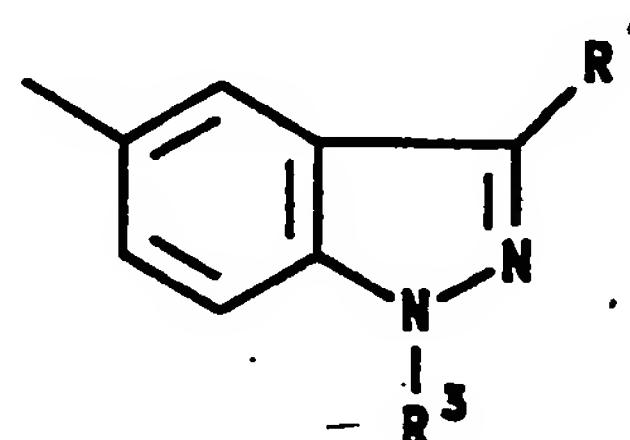
wherein A¹, A², E and F are as defined above. Preferred imidazole, triazole and tetrazole rings of formula I include the rings represented by formulae IA, IB, IC, IG and IJ above.

5 The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or 2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the -NH- moiety, which in turn 10 is connected to the five-membered heteroaromatic ring.

The group F is suitably an indole, benzofuran or benzthiophene moiety of formula FA, or an indazole moiety of formula FB:



(FA)

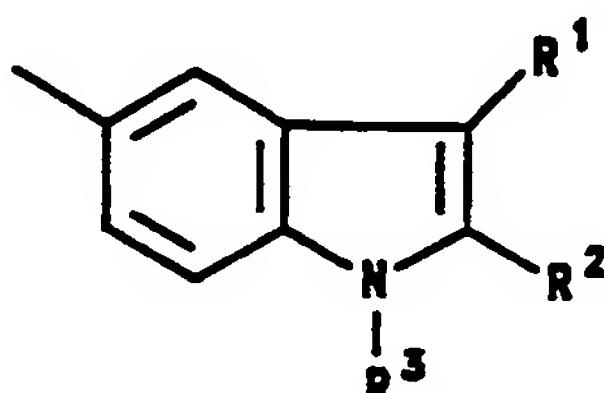


(FB)

wherein B, R¹, R² and R³ are as defined above.

Preferably, the group F represents an indole moiety of structure FC:

25



(FC)

wherein R¹, R² and R³ are as defined above, in particular wherein R² and R³ are both hydrogen.

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It will be appreciated that when all four of W, X, Y and Z represent nitrogen, i.e. when the ring of formula I is a tetrazole ring, then the group A² will be a non-bonded electron pair. Otherwise, A¹ and A² will independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XR^Y, -NR^XCOR^Y, -NR^XCO₂R^Y, -NR^XSO₂R^Y, or -NR²CTN^XR^Y.

Suitable values for the groups A¹ and/or A² include C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy or C₁₋₆ alkylthio, any of which groups may be optionally substituted; and hydrogen, halogen, cyano, trifluoromethyl or -NR^XR^Y, in which R^X and R^Y are as defined above. Examples of optional substituents on the groups A¹ and/or A² suitably include trifluoromethyl, C₁₋₆ alkoxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkyl carbonyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, amino, mono- or di(C₁₋₆)alkylamino, C₂₋₆ alkyl carbonyl amino, 20 aryl carbonyl amino, C₂₋₆ alkoxy carbonyl amino, C₁₋₆ alkylsulphonyl amino, arylsulphonyl amino, C₁₋₆ alkylsulphonylaminomethyl, aminocarbonyl amino, mono- or di(C₁₋₆)alkylaminocarbonyl amino, mono- or diarylaminocarbonyl amino, pyrrolidyl carbonyl amino, 25 aminocarbonyl, mono- or di(C₁₋₆)alkylaminocarbonyl, C₁₋₆ alkylaminosulphonyl, aminosulphonyl methyl, and mono- or di(C₁₋₆)alkylaminosulphonyl methyl.

Particular values of A¹ and/or A² include hydrogen, methyl, methoxymethyl, aminomethyl, 30 dimethylaminomethyl, acetylaminomethyl, benzoylaminomethyl, t-butoxycarbonylaminomethyl, methylsulphonylaminomethyl, phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl, aminoethyl, acetylaminoethyl, benzoylaminoethyl, methoxycarbonyl aminoethyl,

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ethoxycarbonylaminoethyl, t-butoxycarbonylaminoethyl,
methylsulphonylaminoethyl, aminocarbonylaminoethyl,
methylaminocarbonylaminoethyl, t-butylaminocarbonyl-
aminoethyl, phenylaminocarbonylaminoethyl,
5 pyrrolidylcarbonylaminoethyl, cyclopropyl, phenyl,
methylsulphonylaminophenyl, aminocarbonylphenyl,
methylaminocarbonylphenyl, methylsulphonylaminomethyl-
phenyl, aminosulphonylmethylphenyl, methylaminosulphonyl-
methylphenyl, dimethylaminosulphonylmethylphenyl, benzyl,
10 trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl,
methylsulphonylaminobenzyl, aminocarbonylaminobenzyl,
aminocarbonylbenzyl, methylaminocarbonylbenzyl,
methylsulphonylbenzyl, methylaminosulphonylbenzyl,
pyridylmethyl, methoxypyridylmethyl, amino, methylamino,
15 benzylamino, dimethylamino, t-butoxycarbonylamino-
ethylamino and methylsulphonylaminoethylamino.

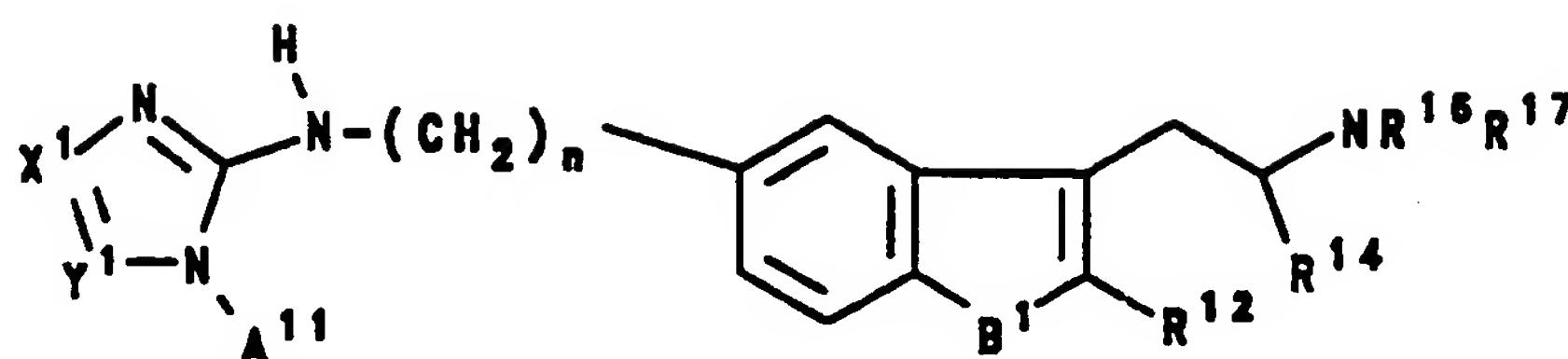
Preferred values of A¹ and/or A² include
hydrogen, methyl, ethyl, benzyl and amino.

Representative values of R¹ include aminoethyl,
20 N-methylaminoethyl, N,N-dimethylaminoethyl, 4-piperidyl,
1-methyl-4-piperidyl, 3-pyrrolidinyl and 1-methyl-3-
pyrrolidinyl.

Preferred values for the groups R² to R⁷ are
hydrogen and methyl.

25 A particular sub-class of compounds according
to the invention is represented by the compounds of
formula IIA, and salts and prodrugs thereof:

- 11 -



(IIA)

wherein

10 X^1 represents nitrogen or A^{12} -C;
 Y^1 represents nitrogen or CH;
 n is zero, 1, 2 or 3;
 B^1 represents oxygen, sulphur or $N-R^{13}$;
 A^{11} and A^{12} independently represent C_{1-6} alkyl,

15 C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl,
aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl,
heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6}
alkylamino or di(C_{1-6})alkylamino, any of which groups may
be optionally substituted; or hydrogen, halogen, cyano,
20 trifluoromethyl or amino; and

R^{12} , R^{13} , R^{14} , R^{16} and R^{17} independently represent
hydrogen or C_{1-6} alkyl.

Examples of optional substituents on the groups
 A^{11} and A^{12} suitably include trifluoromethyl, C_{1-6} alkoxy,
25 C_{2-6} alkoxy carbonyl, C_{2-6} alkyl carbonyl, C_{1-6} alkylsulphonyl,
arylsulphonyl, amino, mono- or di(C_{1-6})alkylamino, C_{2-6}
alkyl carbonyl amino, aryl carbonyl amino, C_{2-6}
30 alkoxy carbonyl amino, C_{1-6} alkylsulphonyl amino, C_{1-6}
arylsulphonyl amino, C_{1-6} alkylsulphonyl amino methyl,
aminocarbonyl amino, mono- or di(C_{1-6})alkylamino-
carbonyl amino, mono- or diarylaminocarbonyl amino,
pyrrolidyl carbonyl amino, aminocarbonyl, mono- or
di(C_{1-6})alkylaminocarbonyl, C_{1-6} alkylaminosulphonyl,

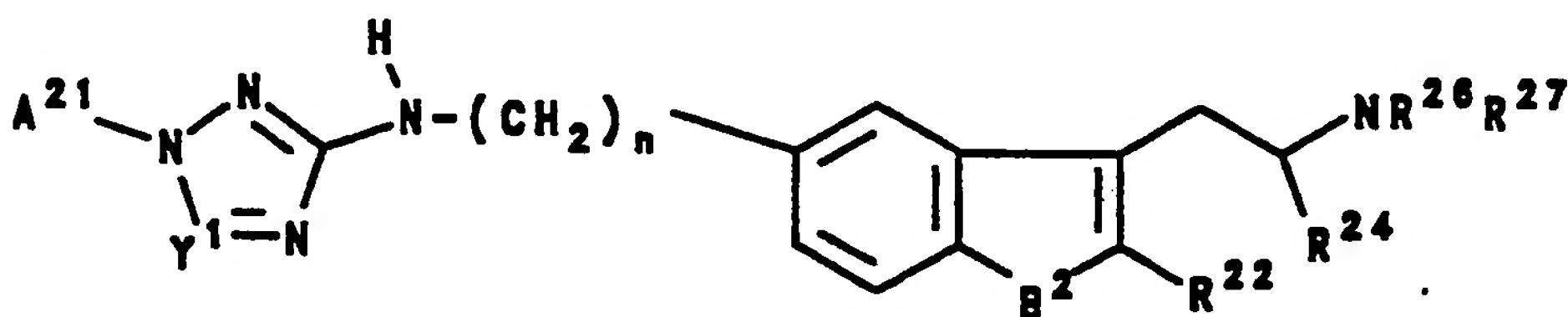
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aminosulphonylmethyl, and mono- or di(C₁₋₆)alkyl-aminosulphonylmethyl.

Particular values of A¹¹ and A¹² with respect to formula IIA include hydrogen, methyl, ethyl, benzyl and amino. When X¹ represents A¹²-C, the group A¹¹ is 5 preferably hydrogen or methyl.

Preferably, R¹², R¹³ and R¹⁴ each represents hydrogen. Preferred values of R¹⁶ and R¹⁷ with respect to formula IIA include hydrogen and methyl.

10 Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



(IIB)

wherein

Y¹ represents nitrogen or A²²-C;

n is zero, 1, 2 or 3;

25 B² represents oxygen, sulphur or N-R²³;

A²¹ and A²² independently represent C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino or di(C₁₋₆)alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

30 R²², R²³, R²⁴, R²⁶ and R²⁷ independently represent hydrogen or C₁₋₆ alkyl.

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Examples of optional substituents on the groups A²¹ and A²² correspond to those indicated for the groups A¹¹ and A¹² with respect to formula IIA above. Particular values of A²¹ and A²² with respect to formula IIB include 5 hydrogen, methyl, ethyl and benzyl.

Preferably, R²², R²³ and R²⁴ each represents hydrogen. Preferred values of R²⁶ and R²⁷ with respect to formula IIB include hydrogen and methyl.

Specific compounds within the scope of the 10 present invention include:
3-[2-(dimethylamino)ethyl]-5-[(2-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole;
3-[2-(dimethylamino)ethyl]-5-[(imidazol-2-yl)-aminomethyl]-1H-indole;
15 3-[2-(dimethylamino)ethyl]-5-[(4-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole;
3-[2-(dimethylamino)ethyl]-5-[(1-methylimidazol-2-yl)aminomethyl]-1H-indole;
3-[2-(dimethylamino)ethyl]-5-[(1-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole;
20 3-[2-(dimethylamino)ethyl]-5-[(1-methyltetrazol-5-yl)amino]-1H-indole;
and salts and prodrugs thereof.

The invention also provides pharmaceutical 25 compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as 30

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tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, 5 dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring 10 to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid 15 preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to 20 provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by 25 an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of 30 polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated

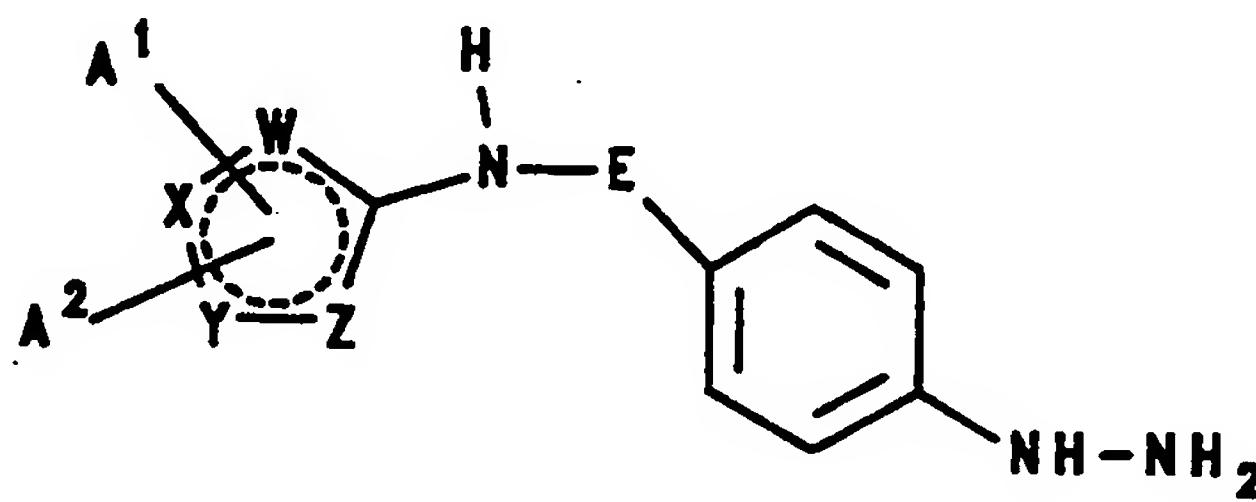
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for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

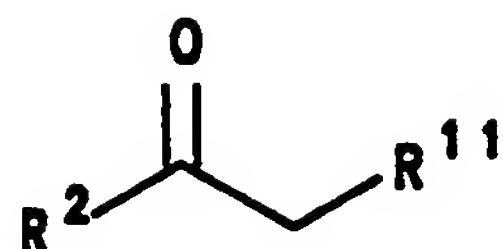
The compounds according to this invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by a process which comprises reacting a compound of formula III:

20



wherein W, X, Y, Z, A¹, A² and E are as defined above; with a compound of formula IV or a carbonyl-protected form thereof:

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(IV)

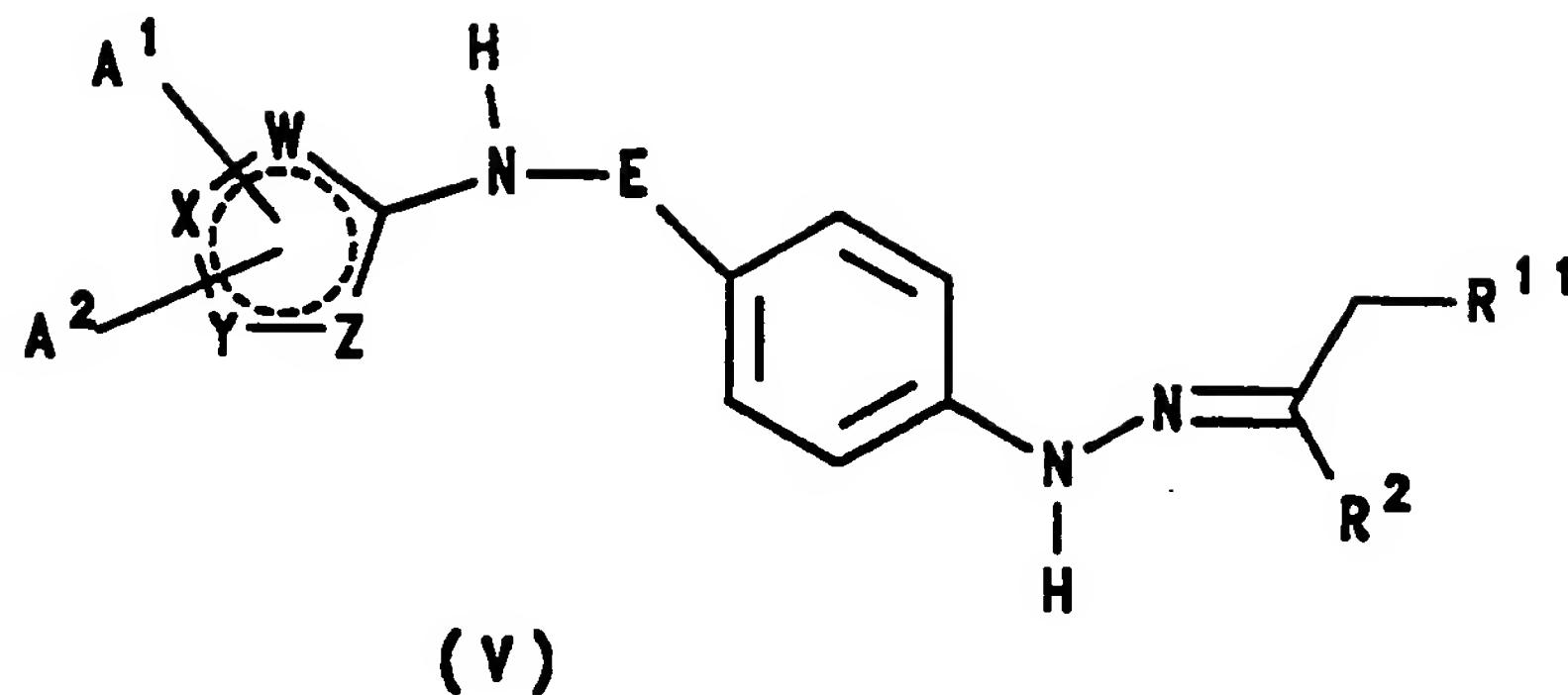
wherein R² is as defined above and R¹¹ corresponds to the group R¹ as defined above or represents a group of formula -CH₂.CHR⁴D¹, in which R⁴ is as defined above and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

10 Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or 15 ketal derivatives.

20 The readily displaceable group D¹ in the compounds of formula IV suitably represents a halogen atom, preferably chlorine. When the moiety R¹¹ in the compounds of formula IV is a group of formula -CH₂.CHR⁴D¹, the substituent D¹ is displaced in situ under the prevailing reaction conditions to afford a final product of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂. The terminal amino group can subsequently, if desired, be further elaborated using techniques known 25 from the art to give a compound of formula I wherein R¹ represents the required group of formula -CH₂.CHR⁴.NR⁶R⁷.

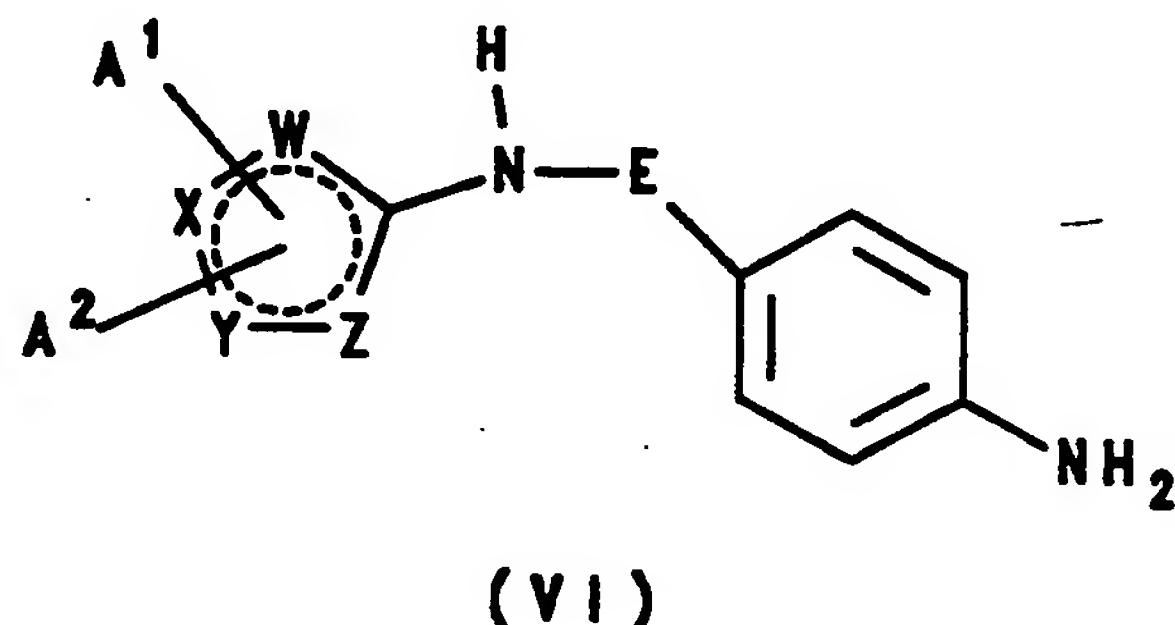
30 The reaction of compounds III and IV may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula V:

- 17 -



wherein W, X, Y, Z, A¹, A², E, R² and R¹¹ are as defined above; followed by cyclisation using a suitable reagent, such as a polyphosphate ester.

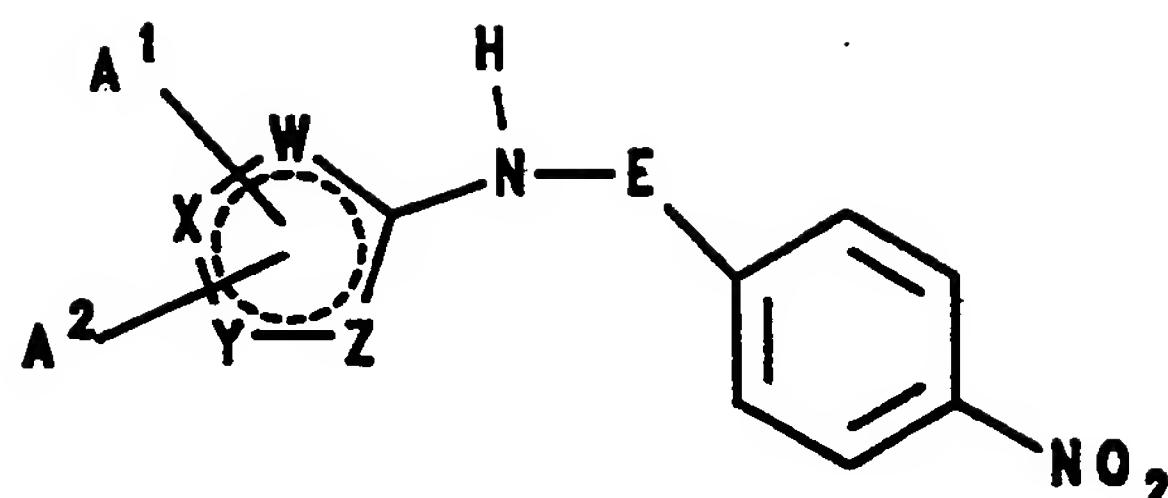
15 The hydrazines of formula III may be prepared from the corresponding anilines of formula VI:



25 wherein W, X, Y, Z, A¹, A² and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced *in situ* using, for example, tin(II) chloride/conc. HCl, sodium sulphite/conc. HCl, or sodium nitrite/conc. H₂SO₄.

30 The anilines of formula VI may be prepared by reduction of the corresponding nitro compounds of formula VII:

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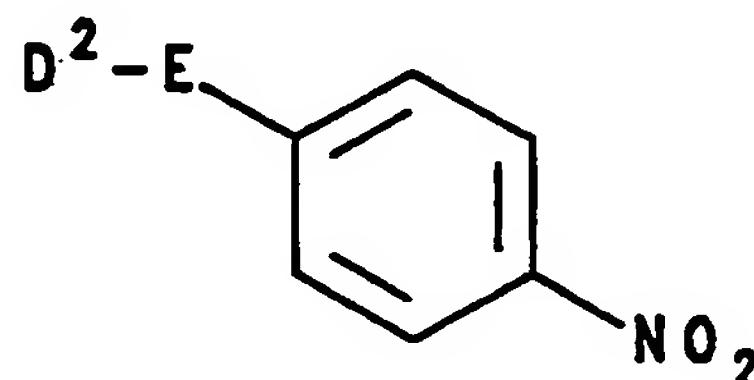
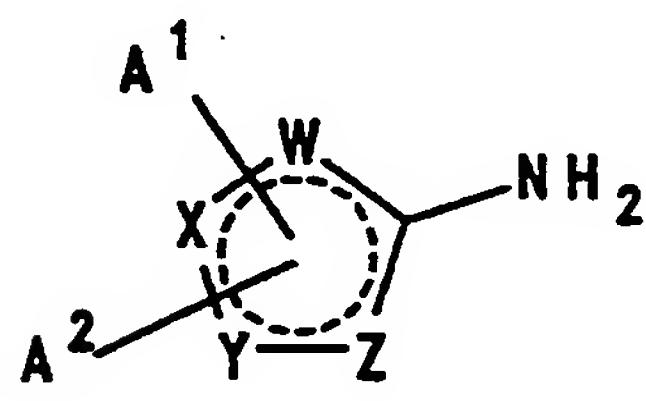


(VII)

10 wherein W, X, Y, Z, A¹, A² and E are as defined above; typically by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or

15 using tin(II) chloride.

The nitro compounds of formula VII may be prepared by a variety of methods which will be readily apparent to those skilled in the art. One such method involves reacting an amino compound of formula VIII with a compound of formula IX:



(VIII)

(IX)

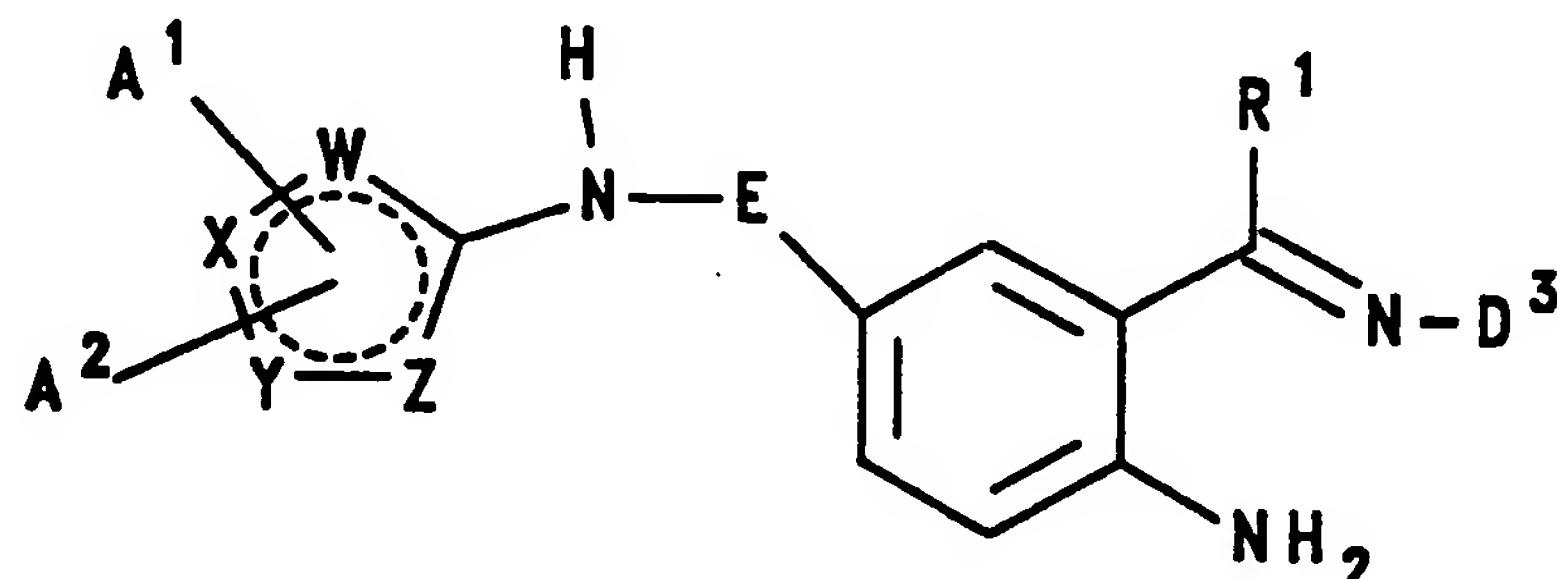
30 wherein W, X, Y, Z, A¹, A² and E are as defined above, and D² represents a readily displaceable group.

The reaction is conveniently carried out in the presence of sodium hydride using N,N-dimethylformamide as solvent.

- 19 -

5 The readily displaceable group D² in the compounds of formula IX is suitably a halogen atom, preferably bromine; except when the moiety D² is attached directly to the aromatic ring, i.e. when E represents a bond, in which case D² is preferably fluorine.

10 The compounds according to the invention wherein the group F is an indazole moiety of structure FB as defined above may be prepared by a process which comprises the cyclisation of a compound of formula X:



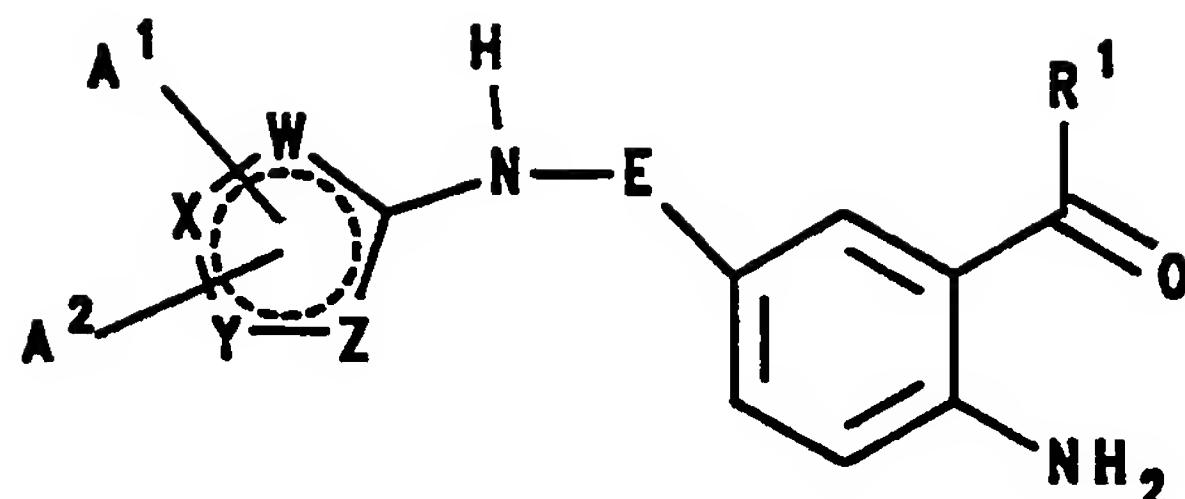
(X)

20 wherein W, X, Y, Z, A¹, A², E and R¹ are as defined above; and D³ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

25 The cyclisation of compound X is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

30 The readily displaceable group D³ in the compounds of formula X suitably represents a C₁₋₄ alkanoyloxy group, preferably acetoxy. Where D³ in the desired compound of formula X represents acetoxy, this compound may be conveniently prepared by treating a carbonyl compound of formula XI:

- 20 -

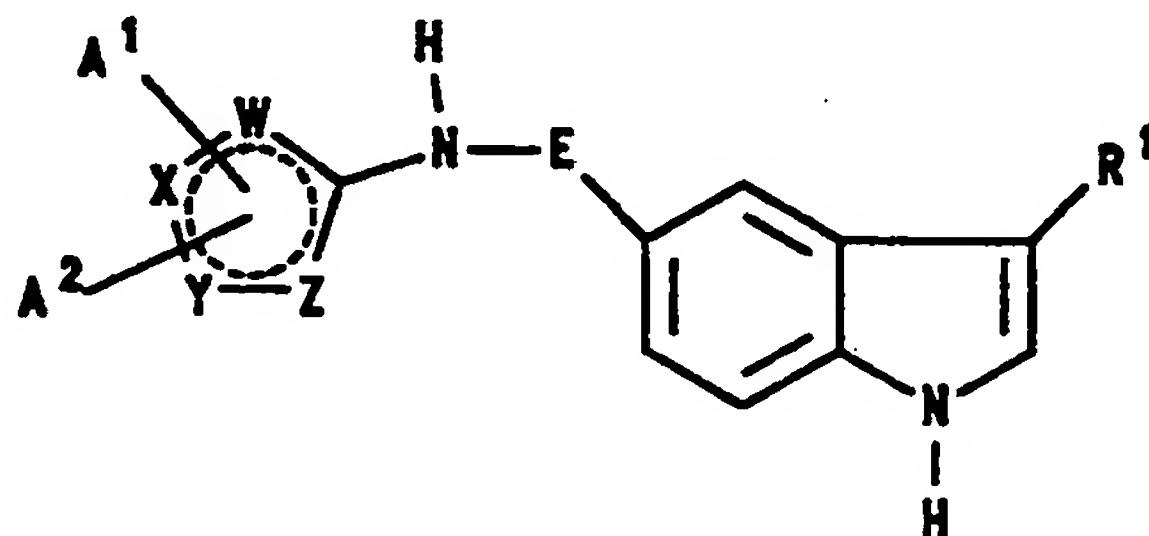


(XI)

10 wherein W, X, Y, Z, A¹, A², E and R¹ are as defined above; or a protected derivative thereof; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

15 The N-formyl protected derivative of the intermediate of formula XI may be conveniently prepared by ozonolysis of an indole derivative of formula XII:

20



(XII)

wherein W, X, Y, Z, A¹, A², E and R¹ are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

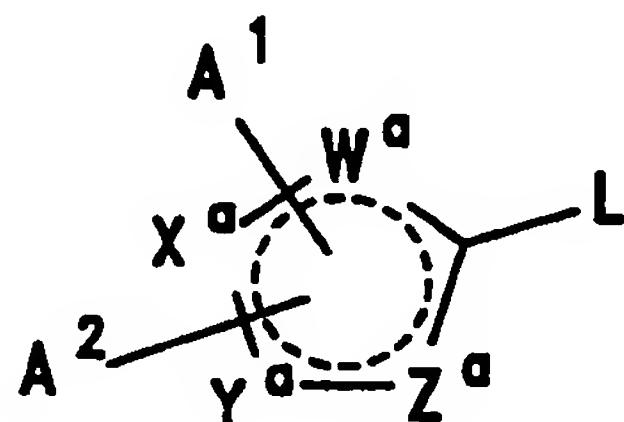
The indole derivative of formula XII may be prepared by methods analogous to those described in the

- 21 -

accompanying Examples, or by procedures well known from the art.

In an alternative process, the triazole compounds according to the invention may be prepared by a method which comprises reacting a compound of formula

5 XIII:



(XIII)

wherein A¹ and A² are as defined above, one of W^a, X^a, Y^a and Z^a represents carbon and the remainder represent nitrogen, and L represents a suitable leaving group; with a compound of formula H₂N-E-F, in which E and F are as defined above.

20 The reaction is conveniently carried out in the presence of an organic base such as diisopropylamine or diisopropylethylamine, in a suitable solvent such as 2-ethoxyethanol or tetrahydrofuran, advantageously at the reflux temperature of the reaction mixture.

25 The leaving group L suitably represents halogen, e.g. chlorine, or a nitro group.

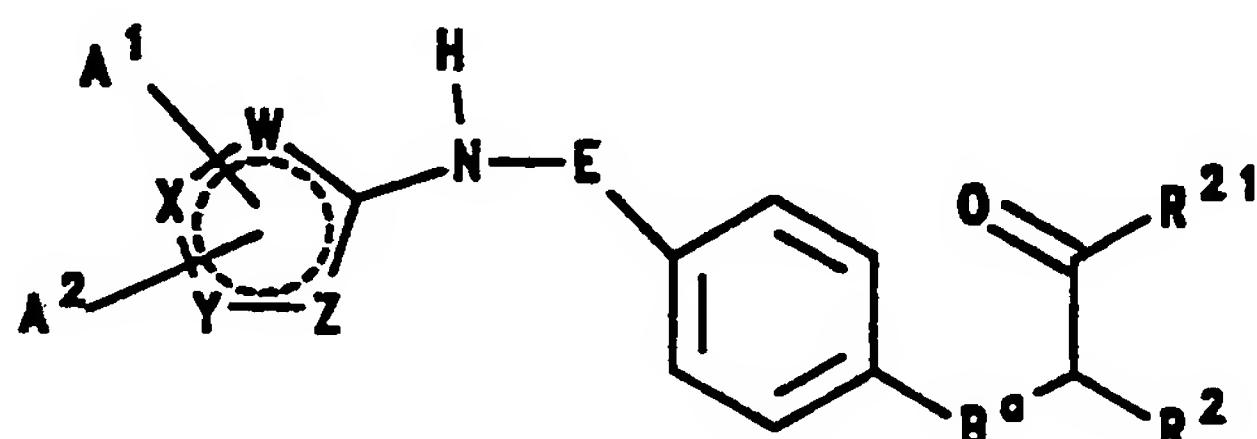
In further process, the compounds according to the invention in which E is other than a chemical bond may be prepared by reacting a compound of formula 30 OHC-E¹-F, wherein F is as previously defined and E¹ represents a bond or a straight or branched alkylene chain containing from 1 to 3 carbon atoms; with a compound of formula VIII as defined above; followed by

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treatment with a reducing agent. The resulting product is a compound of formula I as defined above in which the group E is represented by a moiety of formula $-\text{CH}_2\text{E}'-$.

The above reaction is advantageously carried out in two stages. In the first stage, the reagents are suitably heated together under reflux, with removal of water, in a suitable solvent such as toluene, optionally in the presence of a protic solvent such as ethanol. Removal of water is conveniently effected by standard means such as by the utilisation of 3A molecular sieves, or in a Dean-Stark apparatus. In the second stage, the product obtained from the first stage is treated, preferably crude, with a reducing agent, advantageously in an alcoholic solvent such as methanol. A preferred reducing agent for use in this process is sodium borohydride.

In a yet further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a method which comprises cyclising a compound of formula XIV:



(XIV)

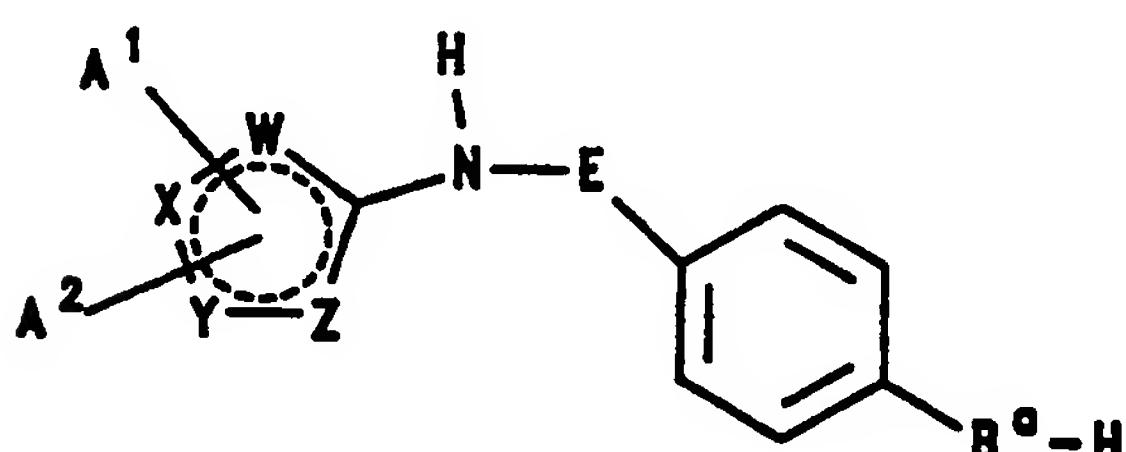
wherein W, X, Y, Z, A¹, A², E and R² are as defined above, B^a represents oxygen or sulphur, and R²¹ corresponds to the group R¹ as defined above or represents a precursor group thereto as discussed below; followed, where

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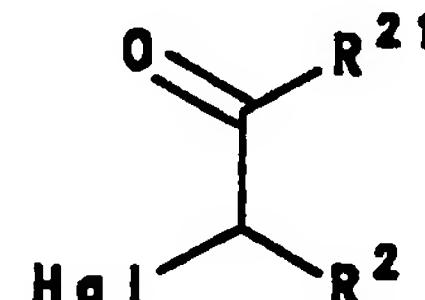
required, by conversion of the group R^{21} into the desired group R^1 by conventional means.

The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XIV may be prepared by reacting a compound of formula XV with a compound of formula XVI:



(XV)

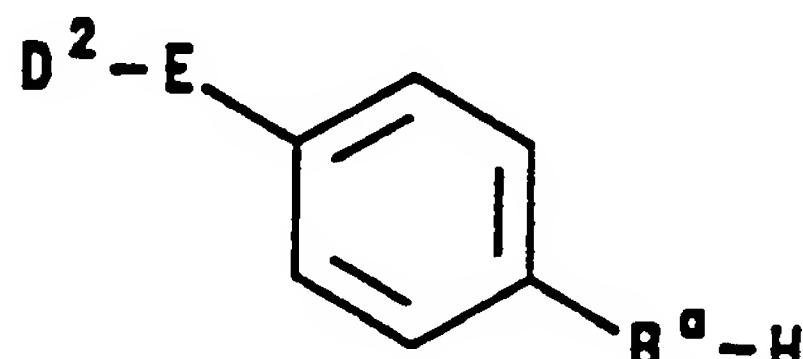


(XVI)

wherein W , X , Y , Z , A^1 , A^2 , E , B^a , R^2 and R^{21} are as defined above, and Hal represents halogen.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XV may be prepared by a variety of methods which will be readily apparent to those skilled in the art. In one such method, a compound of formula VIII as defined above is reacted with a compound of formula XVII:



(XVII)

wherein D^2 , E and B^a are as defined above.

Where they are not commercially available, the intermediates of formula IV, VIII, IX, XIII, XVI, XVII, H₂N-E-F and OHC-E¹-F referred to above may be prepared by methods analogous to those described hereinafter for the preparation of Intermediates 1 to 3; or by procedures known from the art, in particular those described in the literature references cited in the accompanying Examples.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. In particular, a compound of formula I wherein R³ is hydrogen initially obtained may be converted into a compound of formula I wherein R³ represents C₁₋₆ alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide. Similarly, a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂ initially obtained may be converted into a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NR⁶R⁷ in which R⁶ and R⁷ independently represent C₁₋₆ alkyl, by conventional N-alkylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent such as sodium cyanoborohydride.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel

compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-
5 tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.
10

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient 15 subsequent stage using methods known from the art.
20

Alternatively, certain of the functional groups on the desired products may be carried through the reaction sequence as precursor groups, and then regenerated from these precursor groups at a late stage 25 in the overall synthesis. For example, where R¹ in the desired compound of formula I represents a group of formula -(CH₂)₂NH₂, this group can be generated from a cyano precursor -CH₂CN by reduction using, for example, borane/tetrahydrofuran. The cyano precursor may in turn 30 be carried through the reaction sequence as a methyl group -CH₃, which may conveniently be converted to -CH₂CN by treatment with N-bromosuccinimide and benzoyl peroxide, in the presence of a bright light source,

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followed by reaction of the resulting bromo intermediate with sodium cyanide in dimethyl sulphoxide.

The following Examples illustrate the preparation of compounds according to the invention.

5 The ability of test compounds to bind to 5-HT₁-like receptors was measured in membranes prepared from pig caudate using the procedure described in J. Neurosci., 1987, 7, 894. Binding was determined using 2 nM 5-hydroxytryptamine creatinine sulphate,

10 5-[1,2-³H(N)] as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively. The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding (IC₅₀) is below 1 μ M in each case.

15 (IC₅₀) is below 1 μ M in each case.

20 The activity of test compounds as agonists of the 5-HT₁-like receptor was measured in terms of their ability to mediate contraction of the saphenous vein of New Zealand White rabbits, using the procedure described in Arch. Pharm., 1990, 342, 111. Agonist potencies were calculated as -log₁₀EC₅₀ (pEC₅₀) values, from plots of percentage 5-HT (1 μ M) response against the concentration of the agonist. The compounds of the accompanying Examples were found to possess pEC₅₀ values in this assay of not less than 5.0 in each case.

25

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INTERMEDIATE 1

3-[2-(Dimethylamino)ethyl]-1H-indole-5-carboxaldehyde

5 1. 4-Cyanophenylhydrazine. Hydrochloride

To a cooled (-15°C) and stirred suspension of 4-aminobenzonitrile (50g, 423mmol) in concentrated hydrochloric acid (550ml) was added dropwise a solution of sodium nitrite (31.5g, 457mmol) in water (200ml) at such a rate as to maintain the temperature below -10°C. After the addition was finished, the reaction mixture was quickly filtered to remove solids and the filtrate was added portionwise to a cooled (-20°C) and stirred solution of tin (II) chloride dihydrate (477g, 2.1mol) in concentrated hydrochloric acid (370ml) at such a rate as to maintain the temperature below -10°C. After further 15 minutes at -10°C to 0°C, the white precipitate was collected by filtration, washed with diethyl ether (4 x 250ml) and dried to give 56g (78%) of the title compound; mp 235-237°C (ethanol-water 1:1); δ_H (250MHz, DMSO-d₆) 10.50 (3H, br s, -N⁺H₃), 9.10 (1H, br s, -NH-), 7.71 (2H, d, J = 8.8Hz, Ar-H), 7.03 (2H, d, J = 8.8Hz, Ar-H); m/z (CI) 132 (M⁺-1).

25 2. 3-(2-Aminoethyl)-5-cyano-1H-indole. Hydrochloride

To a stirred suspension of 4-cyanophenylhydrazine hydrochloride (50g) in a mixture of ethanol and water (5:1; 2l) was added 4-chlorobutanal dimethylacetal (45g) and the resulting mixture was refluxed for 18 hours. Solvents were removed under vacuum and the residue was azeotroped with toluene to give a brown solid. Crystallisation of this crude material from methanol (150ml) gave 23g (35%) of the title compound as a yellow solid; mp 270-274°C; δ_H (250MHz,

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DMSO-d₆) 11.60 (1H, br s, indole N-H), 8.17 (1H, d, J = 1.1Hz, Ar-H), 7.97 (3H, br s, -N⁺H₃), 7.54 (1H, d, J = 8.5Hz, Ar-H), 7.46 (1H, s, Ar-H), 7.44 (1H, dd, J = 8.5 and 1.1Hz, Ar-H), 3.05 (4H, br s, -CH₂CH₂N-); m/z (CI) 184 (M⁺-1).

5

3. 5-Cyano-3-[2-(dimethylamino)ethyl]-1H-indole

To a cooled (5°C) and stirred solution of sodium methoxide in anhydrous methanol (from 1.75g of sodium metal in 400ml of methanol) was added 3-(2-aminoethyl)-5-cyano-1H-indole hydrochloride (18.6g) and the mixture was stirred for a further 5 minutes before sodium cyanoborohydride (7.2g) and glacial acetic acid (10.4ml) were added. A solution of formaldehyde (37% aqueous solution; 19.9ml) in methanol (50ml) was added dropwise over 30 minutes and the mixture was then allowed to warm to room temperature and stirred for a further 15 minutes. Solvents were removed under vacuum and the residue was diluted with saturated aqueous potassium carbonate (400ml) and products were extracted with ethyl acetate (3 x 400ml). The combined organic extracts were dried (MgSO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 40:8:1) gave 10.5g of the title compound as a pale yellow solid; δ_H (250MHz, CDCl₃) 8.60 (1H, br s, indole N-H), 7.94 (1H, d, J = 1.5Hz, Ar-H), 7.39 (1H, dd, J = 8.5 and 1.5Hz, Ar-H), 7.13 (1H, br d, Ar-H), 2.94 (2H, m, -CH₂-), 2.66 (2H, m, -CH₂-), 2.35 (6H, s, -NMe₂); m/z (FAB) 212 (M⁺-1).

20

4. 3-[2-(Dimethylamino)ethyl]-1H-indole-5-carboxaldehyde

25

To a solution of the product from step 3 (10.5g) in a mixture of water, acetic acid and pyridine (1:1:2; 600ml) were added sodium hypophosphite hydrate (20.6g) and Raney nickel

- 29 -

(50% slurry in water; 5.0g) and the mixture was stirred at 40°C for 24 hours under nitrogen. After being cooled to room temperature, the mixture was filtered and solvents were removed under vacuum. The remaining residue was dissolved in water (300ml), basified to pH 10 with solid potassium carbonate and products were extracted with dichloromethane (3 x 300ml), dried (Na_2SO_4) and concentrated to give the title compound (8.6g) as a pale yellow solid; δ_{H} (360MHz, CDCl_3) 10.04 (1H, s, -CHO), 8.6 (1H, br s, indole N-H), 8.15 (1H, br s, Ar-H), 7.73 (1H, dd, J = 8.5 and 1.4Hz, Ar-H), 7.38 (1H, d, J = 8.5Hz, Ar-H), 7.11 (1H, br s, Ar-H), 3.00 (2H, t, J = 8.2Hz, $-\text{CH}_2-$), 2.69 (2H, t, J = 8.2Hz, $-\text{CH}_2-$), 2.36 (6H, s, $-\text{NMe}_2$).

INTERMEDIATE 2

15

1-tert-Butyloxycarbonyl-3-[2-(dimethylamino)ethyl]-indole-5-carboxaldehyde

20 To a solution of Intermediate 1 (8.4g, 39mmol) in anhydrous acetonitrile (150ml) was added di-tert-butyldicarbonate (12.7g, 58mmol) followed by 4-dimethylaminopyridine (476mg, 3.9mmol) and the resulting mixture was stirred for two hours at room temperature under nitrogen. Solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 90:10:1) to give 10.5g (83%) of the title compound as a viscous oil; δ_{H} (250MHz, CDCl_3) 10.08 (1H, s, -CHO), 8.25 (1H, d, J = 8.6Hz, Ar-H), 8.07 (1H, d, J = 1.5Hz, Ar-H), 7.83 (1H, dd, J = 8.6 and 1.5Hz, Ar-H), 7.50 (1H, s, Ar-H), 2.93 (2H, m, $-\text{CH}_2-$), 2.67 (2H, m, $-\text{CH}_2-$), 2.34 (6H, s, $-\text{NMe}_2$), 1.68 (9H, s, t-Bu).

INTERMEDIATE 3

- 30 -

5-Aminomethyl-3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole

5 1. 3-[2-(N-tert-Butyloxycarbonylamino)ethyl]-5-cyano-1H-indole

To a cooled (-20°C) and stirred suspension of 3-(2-aminoethyl)-5-cyano-1H-indole hydrochloride (15g, 68mmol) in anhydrous dichloromethane (500ml) and anhydrous triethylamine (13.7g, 136mmol) was added di-tert-butyldicarbonate (19.3g, 88mmol). After being stirred at -20°C for 0.5 hours and at room temperature for 1.5 hours, the reaction mixture was diluted with dichloromethane (300ml), washed with 2N hydrochloric acid (300ml), brine (300ml), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol, 96:4) gave 11.3g of the title compound as a white solid; mp 132-134°C (hexane-ethyl acetate); δ_H (250MHz, CDCl₃) 8.42 (1H, br s, indole N-H), 7.93 (1H, s, Ar-H), 7.41 (2H, s, Ar-H), 7.12 (1H, d, J = 2.2Hz, Ar-H), 4.71 (1H, br s, -NH-), 3.44 (2H, q, J = 6.9Hz, -CH₂NH-), 2.94 (2H, t, J = 6.9Hz, Ar-CH₂-), 1.45 (9H, s, t-Bu); m/z (CI) 286 (M⁺+1).

25 2. 5-Aminomethyl-3-[2-(N-tert-butyloxycarbonylamino)ethyl]-1H-indole

A solution of the product from the previous step (11.3g) in a mixture of absolute ethanol (750ml) and chloroform (22ml) was hydrogenated at 50 psi over platinum (IV) oxide (1g) for 28 hours. The catalyst was removed by filtration and solvents were removed under vacuum. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 90:10:1) gave

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9.5g (82%) of the title compound as a white solid; mp 147-149°C (ethyl acetate-diethyl ether); δ_H (360MHz, $CDCl_3$) 8.04 (1H, br s, indole N-H), 7.52 (1H, s, Ar-H), 7.33 (1H, d, $J = 8.4$ Hz, Ar-H), 7.16 (1H, d, $J = 8.4$ Hz, Ar-H), 7.03 (1H, s, Ar-H), 4.61 (1H, br s, -NHBOC), 3.96 (2H, s, Ar- CH_2NH_2), 3.45 (2H, br q, - CH_2NHBOC), 2.95 (2H, t, $J = 6.8$ Hz, Ar- CH_2-), 1.43 (9H, s, t-Bu); m/z (CI) 288 ($M^+ - 1$).

EXAMPLE 1

10 3-[2-(Dimethylamino)ethyl]-5-[(2-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole. Oxalate

15 1. 3-[2-(tert-Butyloxycarbonylamino)ethyl]-5-[(2-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole

20 A solution of Intermediate 3 (250mg, 0.86mmol), 2-methyl-3-nitro-1,2,4-triazole (Khim. Geterotsikl. Soedin., 1970, 6, 259) (132mg, 1.037mmol) and diisopropylamine (300 μ l, 2.15mmol) in 2-ethoxyethanol (3ml) was refluxed under nitrogen for 3 hours before additional diisopropylamine (250 μ l) was added. After further 4 hours at reflux, solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, diethyl ether-methanol-ammonia, 90:10:1) to give 240mg (75%) of the title compound as a thick pale yellow oil; δ_H (250MHz, $CDCl_3$) 8.15 (1H, br s, indole N-H), 7.61 (1H, s, Ar-H), 7.54 (1H, s, triazole-H), 7.35 (1H, d, $J = 8.3$ Hz, Ar-H), 7.24 (1H, d, $J = 8.3$ Hz, Ar-H), 7.06 (1H, s, Ar-H), 4.65 (2H, d, $J = 5.1$ Hz, Ar- CH_2-N), 4.64 (1H, br s, -NHBOC), 4.15 (1H, br s, -NH-), 3.57 (3H, s, -NMe), 3.45 (2H, m, - CH_2NHBOC), 2.94 (2H, t, $J = 6.7$ Hz, Ar- CH_2-), 1.42 (9H, s, t-Bu); m/z (FAB $^+$) 369 ($M^+ - 1$).

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2. 3-(2-Aminoethyl)-5-[(2-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole

5 A solution of the product from the previous step (230mg) in 90% formic acid (10ml) was allowed to stand at room temperature for 1 hour 15 minutes and at 40°C for 30 minutes. Solvents were removed under vacuum and the residue was azeotroped with methanol (10ml) and then purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 10 80:20:2) to give 142mg (85%) of the title compound as a colourless thick oil; δ_{H} (250MHz, DMSO-d₆) 10.70 (1H, s, indole N-H), 7.48 (1H, s, Ar-H), 7.35 (1H, s, triazole-H), 7.26 (1H, d, J = 8.3Hz, Ar-H), 7.10 (1H, s, Ar-H), 7.09 (1H, dd, J = 8.3 and 1.5Hz, Ar-H), 6.80 (1H, t, J = 5.8Hz, -NH-), 4.47 (2H, d, J = 5.8Hz, Ar-CH₂-N), 3.51 (3H, s, -NMe), 2.84-2.68 (4H, m, -CH₂CH₂-); m/z (CI) 271 (M⁺+1).

20 3. 3-[2-(Dimethylamino)ethyl]-5-[(2-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole. Oxalate

25 To a cooled (0°C) and stirred solution of the product from step 2 (135mg, 0.5mmol) in a mixture of methanol (10ml) and glacial acetic acid (142μl) was added sodium cyanoborohydride (63mg, 1.0mmol) followed by a solution of formaldehyde (38% w/v aqueous solution; 99μl) in methanol (2ml) over 3 minutes. The mixture was then allowed to warm to room temperature and it was stirred for 3 hours before saturated aqueous potassium carbonate (3ml) was added and solvents were removed under vacuum. The residue was diluted with water (20ml) and products were extracted with ethyl acetate (2 x 40ml). The combined organic solutions were washed with brine (2 x 10ml), dried (MgSO₄) and concentrated. Flash chromatography of the

- 33 -

residue (silica gel, dichloromethane-methanol-ammonia, 87:13:1.3) gave 123mg (83%) of the title compound free base as a colourless thick oil. The oxalate salt was prepared and recrystallised from a mixture of ethanol and methanol; mp 208-210°C (white needles); δ_{H} (360MHz, DMSO-d₆) 10.91 (1H, s, indole N-H), 7.56 (1H, s, Ar-H), 7.35 (1H, s, triazole-H), 7.31 (1H, d, J = 8.3Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.14 (1H, d, J = 8.3Hz, Ar-H), 6.83 (1H, t, J = 5.1Hz, -NH-), 4.49 (2H, d, J = 5.1Hz, Ar-CH₂-N), 3.52 (3H, s, -NMe), 3.27 (2H, m, -CH₂-), 3.05 (2H, m, -CH₂-), 2.81 (6H, s, -NMe₂); m/z (CI) 299 (M⁺+1). (Found: C, 55.94; H, 6.36; N, 21.46. C₁₆H₂₂N₆ x 1.0 C₂H₂O₄ requires: C, 55.66; H, 6.23; N, 21.64%).

EXAMPLE 2

15 3-[2-(Dimethylamino)ethyl]-5-[imidazol-2-yl]aminomethyl-indole-Tartrate

1. 1-tert-Butyloxycarbonyl-3-[2-dimethylamino)ethyl]-5-[imidazol-2-yl]aminomethyl-indole

20 A mixture of Intermediate 2 (353mg, 1.1mmol), 2-amino-imidazole (180mg, 2.17mmol) and 3Å molecular sieves (500mg) in anhydrous toluene (15ml) and absolute ethanol (5ml) was refluxed under nitrogen for 12 hours. After being cooled to room temperature, solvents were removed under vacuum and the residue was suspended in anhydrous methanol (20ml). Sodium borohydride (200mg) was then added in several portions and stirring was continued for 1 hour at room temperature. The solvent was removed under vacuum and the residue was suspended in saturated aqueous sodium carbonate (30ml) and products were extracted with dichloromethane (3 x 50ml). The combined organic solutions were dried (Na₂SO₄) and

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concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 95:5:0.5) gave 175mg (41%) of the title compound as a yellow solid; δ_H (250MHz, CDCl₃) 8.02 (1H, d, J = 8.4Hz, Ar-H), 7.44 (1H, s, Ar-H), 7.36 (1H, s, Ar-H), 7.22 (1H, dd, J = 8.4 and 1.6Hz, Ar-H), 6.57 (2H, s, Ar-H), 4.45 (2H, s, Ar-CH₂-N), 2.80 (2H, m, -CH₂-), 2.60 (2H, m, -CH₂-), 2.29 (6H, s, -NMe₂), 1.65 (9H, s, t-Bu); m/z (CI) 384 (M⁺+1).

10 2. 3-[2-(Dimethylamino)ethyl]-5-[imidazol-2-yl]amino-
methyl-1H-indole. Tartrate

15 A solution of the product from the previous step (170mg) in 90% formic acid (5ml) was stirred at 40°C for 1 hour under nitrogen. Solvents were removed under vacuum and the residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 90:10:1) to give 52mg of the title compound free base as a thick yellow oil. The tartrate salt was prepared and recrystallised from methanol; mp 198-200°C; δ_H (360MHz, D₂O) 7.67 (1H, s, Ar-H), 7.56 (1H, d, J = 8.4Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.29 (1H, d, J = 8.4Hz, Ar-H), 6.80 (2H, s, Ar-H), 4.63 (2H, s, Ar-CH₂-N), 4.33 (2H, s, tartaric acid), 3.50 (2H, t, J = 7.4Hz, -CH₂-), 3.27 (2H, t, J = 7.4Hz, -CH₂-), 2.93 (6H, s, -NMe₂); m/z (CI) 284 (M⁺+1). (Found: C, 52.03; H, 6.18; N, 15.63. C₁₆H₂₁N₅ x 1.0 C₄H₆O₆ x 1.4 H₂O requires: C, 52.37; H, 6.55; N, 15.27%).

EXAMPLE 3

30 3-[2-(Dimethylamino)ethyl]-5-[4-methyl-1,2,4-triazol-3-yl]
aminomethyl-1H-indole. Oxalate

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1. 1-tert-Butyloxycarbonyl-3-[2-(dimethylamino)ethyl]-5-[4-methyl-1,2,4-triazol-3-yl]aminomethylindole

The title compound was prepared from Intermediate 2 and 5 3-amino-4-methyl-1,2,4-triazole (Chem. Ber., 1964, 97, 396) using a similar method to that described for Example 2 (step 1); thick yellow oil; δ_H (250MHz, $CDCl_3$) 8.07 (1H, d, J = 8.4Hz, Ar-H), 7.72 (1H, s, Ar-H), 7.57 (1H, s, Ar-H), 7.42 (1H, s, Ar-H), 10 7.35 (1H, dd, J = 8.4 and 1.5Hz, Ar-H), 4.66 (2H, d, J = 5.5Hz, Ar- CH_2 -N), 4.26 (1H, br t, -NH-), 3.40 (3H, s, -NMe), 2.87 (2H, m, - CH_2 -), 2.66 (2H, m, - CH_2 -), 2.36 (6H, s, -NMe₂), 1.67 (9H, s, t-Bu); m/z (CI) 399 ($M^+ + 1$).

15. 2. 3-[2-(Dimethylamino)ethyl]-5-[4-methyl-1,2,4-triazol-3-yl]aminomethyl-1H-indole. Oxalate

The title compound free base was prepared from the product of the previous step using a similar method to that described for Example 2 (step 2). The oxalate salt was prepared; 20 mp 170-172°C (methanol-diethyl ether); δ_H (360MHz, D_2O) 8.18 (1H, s, Ar-H), 7.68 (1H, s, Ar-H), 7.54 (1H, d, J = 8.4Hz, Ar-H), 7.37 (1H, s, Ar-H), 7.28 (1H, d, J = 8.4Hz, Ar-H), 4.67 (2H, s, Ar- CH_2 -N), 3.58 (3H, s, -NMe), 3.50 (2H, t, J = 7.4Hz, - CH_2 -), 3.25 (2H, t, J = 7.4Hz, - CH_2 -), 2.91 (6H, s, -NMe₂); m/z (CI) 299 (25 $M^+ + 1$). (Found: C, 48.06; H, 5.66; N, 16.32. $C_{16}H_{22}N_6 \times 2.3 C_2H_2O_4 \times 0.5 H_2O$ requires: C, 48.09; H, 5.41; N, 16.34%).

EXAMPLE 4

30. 3-[2-(Dimethylamino)ethyl]-5-[1-methylimidazol-2-yl]amino methyll-1H-indole. Tartrate

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A mixture of Intermediate 1 (115mg, 0.53mmol) and 2-amino-1-methylimidazole (80mg, 0.82mmol) in anhydrous toluene (8ml) was refluxed for 10 hours under nitrogen, using a Dean-Stark trap. After being cooled to room temperature, the solvent was removed under vacuum and the residue was redissolved in anhydrous methanol (5ml). Solid sodium borohydride (350mg) was added in several portions over 30 minutes and the mixture was stirred for a further 1.5 hours at room temperature. The solvent was removed under vacuum, the residue was suspended in saturated aqueous sodium carbonate and products were extracted with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated to a yellow oil. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 95:5:0.5 to 90:10:1) gave 110mg (70%) of the title compound free base. The tartrate salt was prepared; mp 119-121°C (methanol-diethyl ether); δ_{H} (360MHz, D_2O) 7.67 (1H, s, Ar-H), 7.55 (1H, d, J = 8.4Hz, Ar-H), 7.38 (1H, s, Ar-H), 7.29 (1H, dd, J = 8.4 and 1.4Hz, Ar-H), 6.80 (2H, m, Ar-H), 4.66 (2H, s, Ar- $\text{CH}_2\text{-N}$), 4.33 (2H, s, tartaric acid), 3.50 (3H, s, -NMe), 3.50 (2H, t, J = 7.3Hz, - $\text{CH}_2\text{-}$), 3.26 (2H, t, J = 7.3Hz, - $\text{CH}_2\text{-}$), 2.93 (6H, s, -NMe₂); m/z (EI) 297 (M^+). (Found: C, 52.94; H, 6.85; N, 14.09. $\text{C}_{17}\text{H}_{23}\text{N}_5 \times 1.05 \text{C}_4\text{H}_6\text{O}_6 \times 1.6\text{H}_2\text{O}$ requires C, 52.63; H, 6.77; N, 14.48%).

25

EXAMPLE 5

3-[2-(Dimethylamino)ethyl]-5-[(1-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole. Oxalate

30 The title compound free base was prepared in 17% isolated yield from Intermediate 1 and 3-amino-1-methyl-1,2,4-triazole (Bull. Soc. Chim. Fr., 1973, 1849) using a similar method to that

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described for Example 4. The oxalate salt was prepared and recrystallised from methanol; mp 185°C; δ_H (360MHz, D₂O) 8.09 (1H, s, Ar-H), 7.62 (1H, s, Ar-H), 7.49 (1H, d, J = 8.3Hz, Ar-H), 7.53 (1H, s, Ar-H), 7.26 (1H, dd, J = 8.3 and 1.4Hz, Ar-H), 4.49 (2H, s, Ar-CH₂-N), 3.71 (3H, s, -NMe), 3.47 (2H, t, J = 7.4Hz, -CH₂-), 3.22 (2H, t, J = 7.4Hz, -CH₂-), 2.90 (6H, s, -NMe₂); m/z (EI) 298 (M⁺). (Found: C, 55.30; H, 6.22; N, 21.23. C₁₆H₂₁N₆ x 1.0 C₂H₂O₄ x 0.2H₂O requires: C, 55.29; H, 6.03; N, 21.49%).

10

EXAMPLE 6

3-[2-(Dimethylamino)ethyl]-5-[1-methyltetrazol-5-yl]aminol-1H-indole. Oxalate

1. 4-[1-Methyltetrazol-5-yl]aminolnitrobenzene

15 To a stirred suspension of 1-methyl-5-aminotetrazole (4.8g, 48.5mmol) in anhydrous dimethylformamide (60ml) was added portionwise sodium hydride (80% dispersion in oil, 2.18g), under a nitrogen atmosphere. After 15 minutes, a solution of 1-fluoro-4-nitrobenzene (6.84g, 48.4mmol) in anhydrous dimethylformamide (20ml) was added dropwise over 30 minutes and the deep red mixture was stirred for 16 hours at room temperature. Water (500ml) was carefully added followed by 4N sodium hydroxide (50ml) and the basic aqueous solution was extracted with diethyl ether (2 x 400ml). The ethereal phases were washed with 1N sodium hydroxide (3 x 50ml) and the combined basic aqueous solutions were acidified with 5N hydrochloric acid. The resultant off white precipitate was collected by filtration, washed with water and dried to afford 6.3g (59%) of the title compound; δ_H (360MHz, DMSO-d₆) 10.15 (1H, br s, -NH-), 8.27 (2H, d, J = 7.0Hz, Ar-H), 7.86 (2H, d, J = 7.0Hz, Ar-H), 3.99 (3H, s, -NMe).

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2. 4-[(1-Methyltetrazol-5-yl)aminol]aniline

A solution of 4-[(1-methyltetrazol-5-yl)amino]nitrobenzene (2.0g) in glacial acetic acid (200ml) was hydrogenated at 45 psi over 10% palladium on carbon (200mg) for 2 hours 45 minutes. The catalyst was filtered off and solvents were removed under vacuum. The remaining residue was triturated with diethyl ether to give 1.49g (87%) of the title compound as a white solid; δ_H (360MHz, DMSO-d₆) 8.74 (1H, br s, -NH-), 7.24 (2H, d, J = 8.6Hz, Ar-H), 6.55 (2H, d, J = 8.6Hz, Ar-H), 4.80 (2H, br s, -NH₂), 3.84 (3H, s, -NMe).

3. 3-[2-(Dimethylamino)ethyl]-5-[(1-methyltetrazol-5-yl)aminol- 1H-indole. Oxalate

To a cooled (0°C) and stirred suspension of 4-(1-methyltetrazol-5-yl)amino]aniline (1.7g, 8.9mmol) in concentrated hydrochloric acid (13.6ml) was added dropwise a solution of sodium nitrite (680mg) in water (7.8ml) at such a rate as to maintain the temperature below 5°C. After the addition was completed, the mixture was stirred for a further 30 minutes at 0°C and quickly filtered to remove solids. The resulting filtrate was added portionwise to a cooled (-10°C) and stirred solution of tin (II) chloride dihydrate (8.0g, 35.4mmol) in concentrated hydrochloric acid (10ml) at such a rate as to maintain the temperature below -5°C. After a further 30 minutes at -5°C, the mixture was allowed to warm to room temperature. Addition of 10N sodium hydroxide (3ml) gave a white precipitate which was collected by filtration, washed with water and dried under high vacuum to afford 4-[(1-methyltetrazol-5-yl)amino]phenylhydrazine hydrochloride (728mg, 34%); a second crop (460mg, 21%) was obtained by

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addition of more 10N sodium hydroxide (2ml) to the mother liquors.

To a solution of 4-[(1-methyltetrazol-5-yl)amino] phenylhydrazine hydrochloride (1.1g) in 4% aqueous sulfuric acid (40ml) was added 4-dimethylaminobutanal dimethylacetal (870mg) and the mixture was stirred at room temperature for 30 minutes and then refluxed for 1 hour. After being cooled to 0°C, the mixture was basified with saturated aqueous potassium carbonate and products were extracted with ethyl acetate (3 x 100ml). The combined organic solutions were dried (MgSO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 60:8:1) gave 350mg (27%) of the title compound free base. The oxalate salt was prepared; mp 146-148°C (methanol-diethyl ether); δ_{H} (360MHz, D_2O) 7.63 (1H, d, J = 2.0Hz, Ar-H), 7.48 (1H, d, J = 8.7Hz, Ar-H), 7.32 (1H, s, Ar-H), 7.16 (1H, dd, J = 8.7 and 2.0Hz, Ar-H), 3.82 (3H, s, -NMe), 3.44 (2H, t, J = 7.5Hz, - CH_2 -), 3.34 (3H, s, CH_3OH), 3.17 (2H, t, J = 7.5Hz, - CH_2 -), 2.89 (6H, s, -NMe₂); m/z (CI) 286 ($\text{M}^+ + 1$). (Found: C, 53.41; H, 6.46; N, 26.82. $\text{C}_{14}\text{H}_{19}\text{N}_7$ x CH_4O x 0.5 $\text{C}_2\text{H}_2\text{O}_4$ requires: C, 53.03; H, 6.68; N, 27.05%).

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EXAMPLE 7

Tablet Preparation

5 Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compounds are prepared as illustrated below:

10 3-[2-(Dimethylamino)ethyl]-5-[(2-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole. Oxalate

15 3-[2-(Dimethylamino)ethyl]-5-[(imidazol-2-yl)aminomethyl]-1H-indole. Tartrate

20 3-[2-(Dimethylamino)ethyl]-5-[(4-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole. Oxalate

25 3-[2-(Dimethylamino)ethyl]-5-[(1-methylimidazol-2-yl)aminomethyl]-1H-indole. Tartrate

30 3-[2-(Dimethylamino)ethyl]-5-[(1-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole. Oxalate

35 3-[2-(Dimethylamino)ethyl]-5-[(1-methyltetrazol-5-yl)amino]-1H-indole. Oxalate

TABLE FOR DOSES CONTAINING FROM
1-25MG OF THE ACTIVE COMPOUND

	Amount-mg		
	Active Compound	1.0	2.0
25	Microcrystalline cellulose	49.25	48.75
	Modified food corn starch	49.25	48.75
	Magnesium stearate	0.50	0.50

TABLE FOR DOSES CONTAINING FROM
26-100MG OF THE ACTIVE COMPOUND

Active Compound	26.0	50.0	100.0
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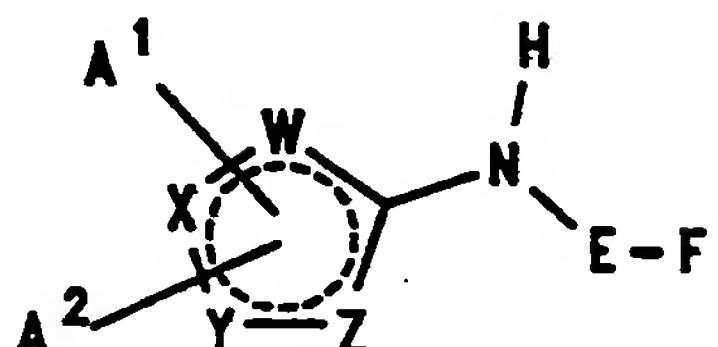
Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

5 All of the active compound, cellulose, and a portion of the
corn starch are mixed and granulated to 10% corn starch paste.
The resulting granulation is sieved, dried and blended with the
remainder of the corn starch and the magnesium stearate. The
resulting granulation is then compressed into tablets containing
10 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active
ingredient per tablet.

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CLAIMS:

1. A compound of formula I, or a salt or
5 prodrug thereof:



(1)

wherein the broken circle represents two non-adjacent
15 double bonds in any position in the five-membered ring;

two, three or four of W, X, Y and Z represent
nitrogen and the remainder represent carbon provided
that, when two of W, X, Y and Z represent nitrogen and
the remainder represent carbon, then the said nitrogen
20 atoms are in non-adjacent positions within the five-
membered ring;

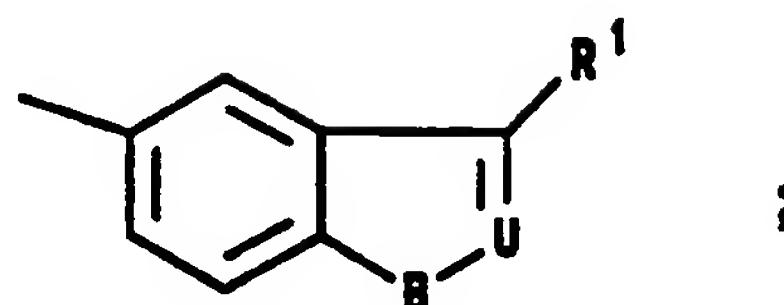
A¹ represents hydrogen, hydrocarbon, a
heterocyclic group, halogen, cyano, trifluoromethyl,
-OR^x, -SR^x, -NR^xR^y, -NR^xCORY, -NR^xCO₂R^y, -NR^xSO₂R^y, or
25 -NR^xCTNR^xR^y;

A² represents a non-bonded electron pair when
all four of W, X, Y and Z represent nitrogen; or, when
two or three of W, X, Y and Z represent nitrogen and the
remainder represent carbon, A² represents hydrogen,
30 hydrocarbon, a heterocyclic group, halogen, cyano,
trifluoromethyl, -OR^x, -SR^x, -NR^xR^y, -NR^xCORY, -NR^xCO₂R^y,
-NR^xSO₂R^y, or -NR^xCTNR^xR^y;

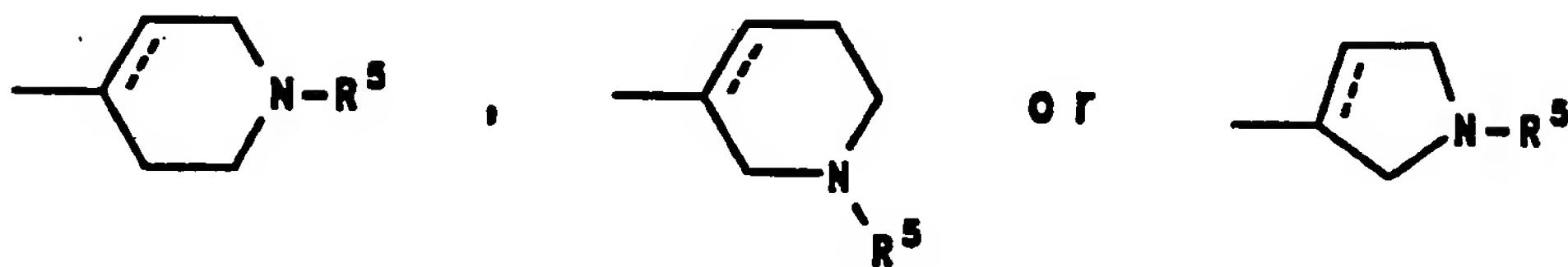
E represents a bond or a straight or branched
alkylene chain containing from 1 to 4 carbon atoms;

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F represents a group of formula



10 U represents nitrogen or C-R²;
 B represents oxygen, sulphur or N-R³;
 R¹ represents -CH₂.CHR⁴.NR⁶R⁷ or a group of
 formula



in which the broken line represents an optional chemical bond;

25 R², R³, R⁴, R⁵, R⁶ and R⁷ independently represent
 hydrogen or C₁₋₆ alkyl;

R^x and R^y independently represent hydrogen,
 hydrocarbon or a heterocyclic group, or R^x and R^y together
 represent a C₂₋₆ alkylene group;

30 R^z represents hydrogen, hydrocarbon or a
 heterocyclic group;

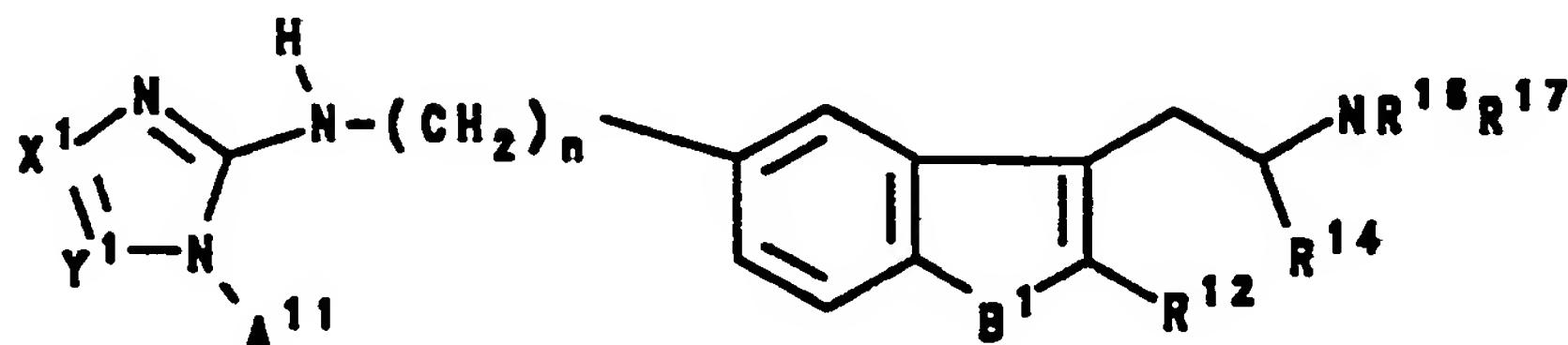
T represents oxygen, sulphur or a group of
 formula =N.G; and

G represents hydrocarbon, a heterocyclic group
 or an electron-withdrawing group.

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2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:

5



(IIA)

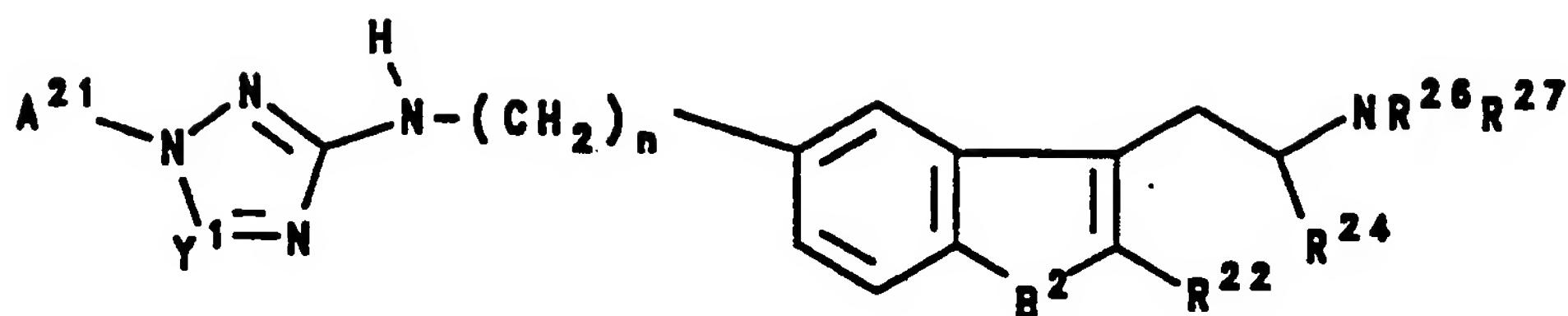
wherein

15 X^1 represents nitrogen or A^{12} -C;
 Y^1 represents nitrogen or CH;
 n is zero, 1, 2 or 3;
 B^1 represents oxygen, sulphur or $N-R^{13}$;
 A^{11} and A^{12} independently represent C_{1-6} alkyl,
 C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl,
20 aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl,
heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6}
alkylamino or di(C_{1-6})alkylamino, any of which groups may
be optionally substituted; or hydrogen, halogen, cyano,
trifluoromethyl or amino; and
25 R^{12} , R^{13} , R^{14} , R^{16} and R^{17} independently represent
hydrogen or C_{1-6} alkyl.

A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:

30

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(11B)

10 wherein

Y¹ represents nitrogen or A²²-C;

n is zero, 1, 2 or 3;

B² represents oxygen, sulphur or N-R²³;A²¹ and A²² independently represent C₁₋₆ alkyl,15 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino or di(C₁₋₆)alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and20 R²², R²³, R²⁴, R²⁶ and R²⁷ independently represent hydrogen or C₁₋₆ alkyl.

25 4. A compound as claimed in claim 1 selected from:

3-[2-(dimethylamino)ethyl]-5-[(2-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole;

3-[2-(dimethylamino)ethyl]-5-[(imidazol-2-yl)-aminomethyl]-1H-indole;

30 3-[2-(dimethylamino)ethyl]-5-[(4-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole;

3-[2-(dimethylamino)ethyl]-5-[(1-methylimidazol-2-yl)aminomethyl]-1H-indole;

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3-[2-(dimethylamino)ethyl]-5-[(1-methyl-1,2,4-triazol-3-yl)aminomethyl]-1H-indole;

3-[2-(dimethylamino)ethyl]-5-[(1-methyltetrazol-5-yl)amino]-1H-indole;

5 and salts and prodrugs thereof.

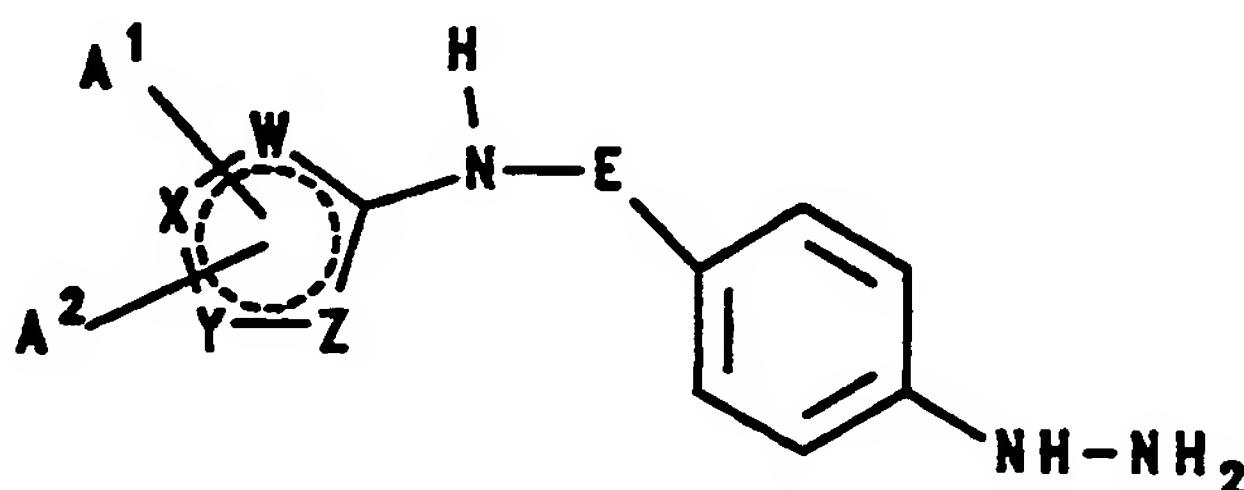
5. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier or excipient.

10 6. A compound as claimed in any one of claims 1 to 4 for use in therapy.

15 7. The use of a compound as claimed in any one of claims 1 to 4 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT₁-like receptors is indicated.

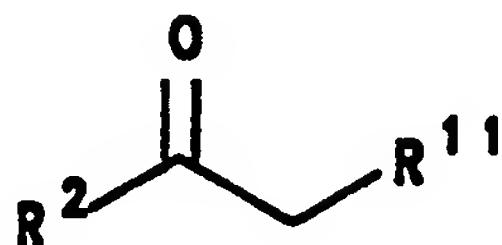
20 8. A process for the preparation of a compound as claimed in any one of claims 1 to 4 which comprises:

25 (A) reacting a compound of formula III:



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wherein W, X, Y, Z, A¹, A² and E are as defined in claim 1; with a compound of formula IV or a carbonyl-protected form thereof:

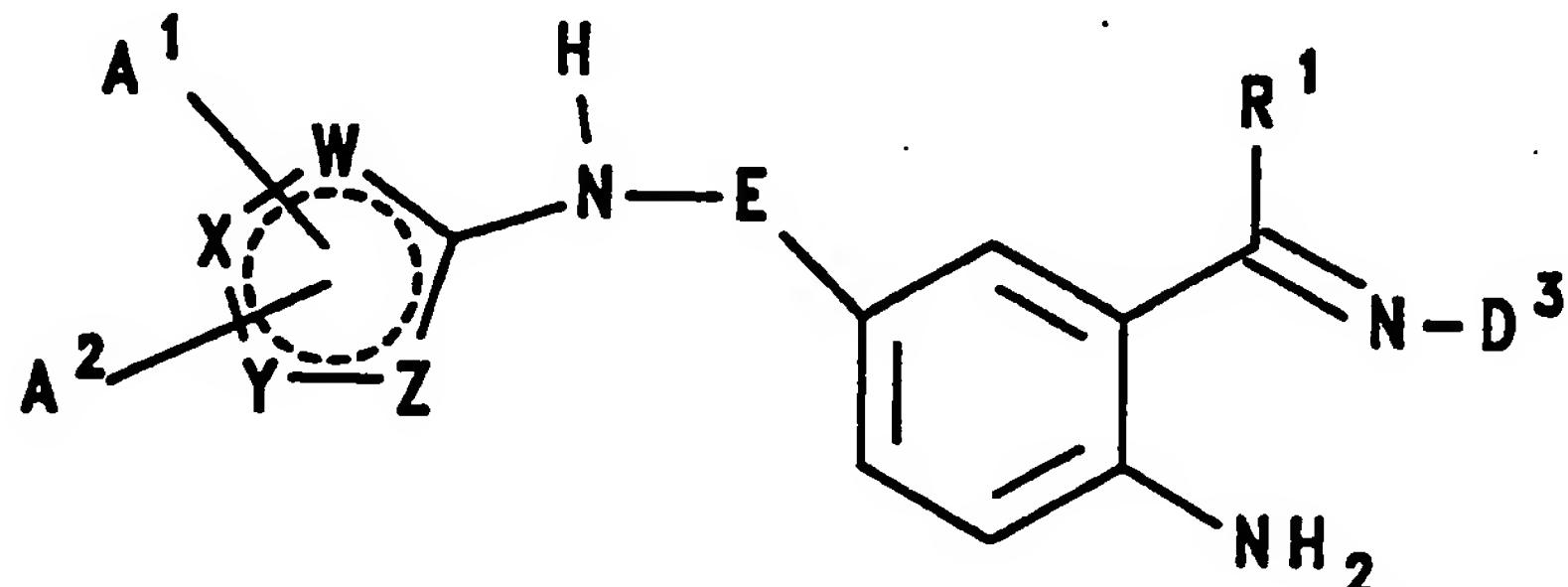


(IV)

10 wherein R² is as defined in claim 1 and R¹¹ corresponds to the group R¹ as defined in claim 1 or represents a group of formula -CH₂.CHR⁴D¹, in which R⁴ is as defined in claim 1 and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; or

15

(B) the cyclisation of a compound of formula X:

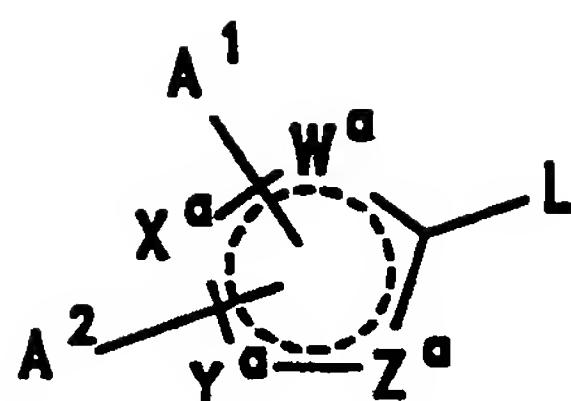


(X)

wherein W, X, Y, Z, A¹, A², E and R¹ are as defined in claim 1, and D³ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; or

(C) reacting a compound of formula XIII:

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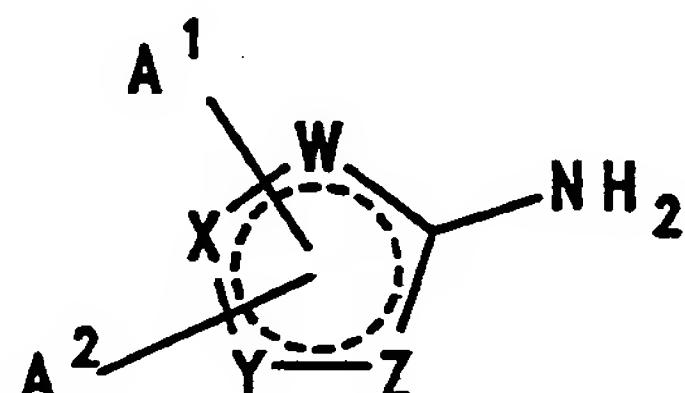
(XIII)

10 wherein A¹ and A² are as defined in claim 1, one of W^a, X^a, Y^a and Z^a represents carbon and the remainder represent nitrogen, and L represents a suitable leaving group; with a compound of formula H₂N-E-F, in which E and F are as defined in claim 1; or

15

(D) reacting a compound of formula OHC-E¹-F, wherein F is as defined in claim 1 and E¹ represents a bond or a straight or branched alkylene chain containing from 1 to 3 carbon atoms, with a compound of formula

20 VIII:

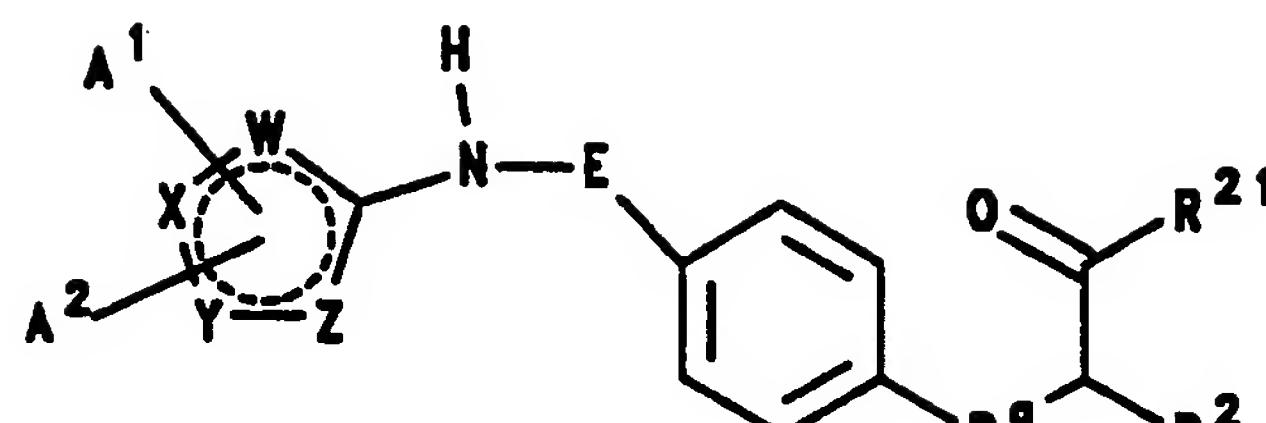


(VIII)

30 wherein W, X, Y, Z, A¹ and A² are as defined in claim 1; followed by treatment with a reducing agent; or

(E) cyclising a compound of formula XIV:

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(XIV)

wherein W, X, Y, Z, A¹, A², E and R² are as defined in
 10 claim 1, B⁰ represents oxygen or sulphur, and R²¹
 corresponds to the group R¹ as defined in claim 1 or
 represents a precursor group thereto; followed, where
 required, by conversion of the group R²¹ into the desired
 group R¹ by conventional means; and

15

(F) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

20

9. A method for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT₁-like receptors is indicated, which method comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

25

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/00652

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D403/12; C07D405/12; C07D409/12; A61K31/41
A61K31/415

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claims No. ¹³
Y	EP,A,0 438 230 (MERCK SHARP & DOHME LTD) 24 July 1991 *whole document* ---	1-8
P,Y	EP,A,0 497 512 (MERCK SHARP & DOHME) 5 August 1992 *see whole document* ---	1-8
A	EP,A,0 313 397 (THE WELLCOME FOUNDATION LIMITED) 26 April 1989 ---	1-8
Y	WO,A,9 118 897 (THE WELLCOME FOUNDATION LIMITED) 12 December 1991 ---	1-8
A	US,A,4 785 016 (GLAXO GROUP LIMITED) 15 November 1988 ---	1-8
		-/-

¹⁰ Special categories of cited documents :

- ¹¹ "A" document defining the general state of the art which is not considered to be of particular relevance
- ¹² "E" earlier document but published on or after the international filing date
- ¹³ "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ¹⁴ "O" document referring to an oral disclosure, use, exhibition or other means
- ¹⁵ "P" document published prior to the international filing date but later than the priority date claimed

- ¹⁶ "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- ¹⁷ "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- ¹⁸ "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- ¹⁹ "Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

28 JUNE 1993

Date of Mailing of this International Search Report

14.07.93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

SCRUTON-EVANS I.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9300652
SA 72673

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 28/06/93

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